FUTURE THERAPEUTIC STRATEGIES FOR DAAs

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Current Issues

Efficacy: 90 – 95%

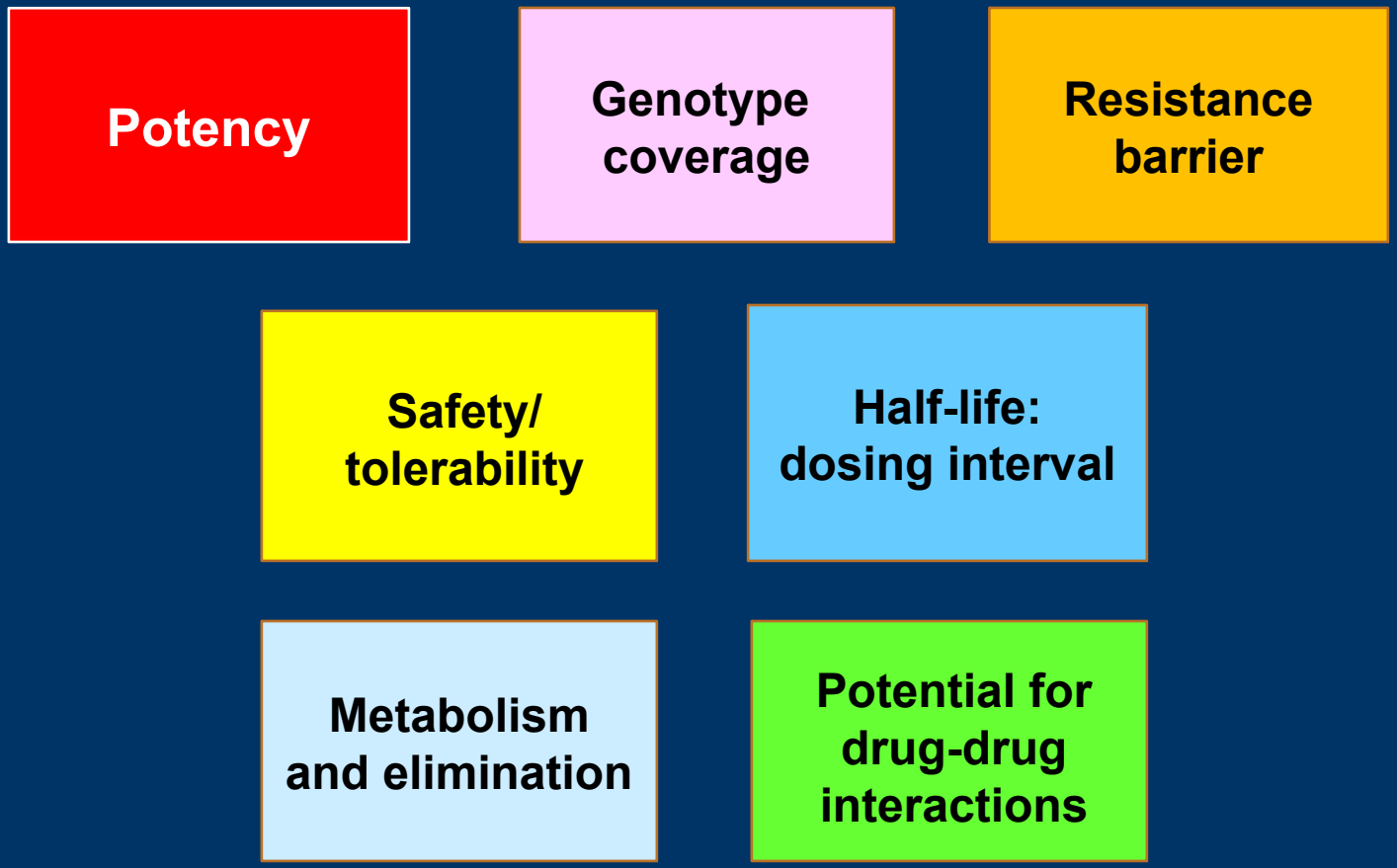
Duration: 6, 8, 12 or 24 weeks

Relapse approaches – salvage therapy

Special populations – are there any?

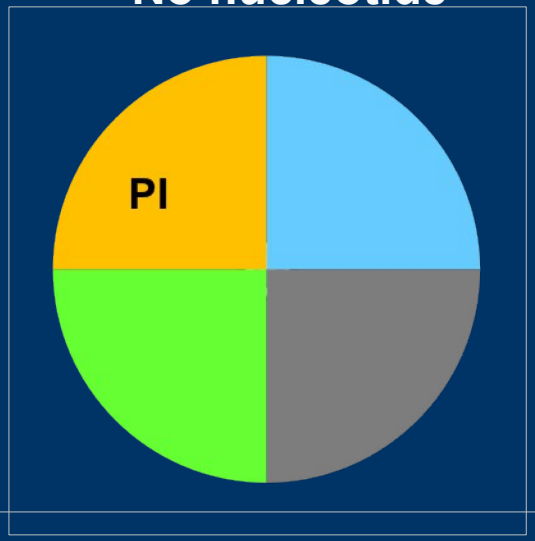
Future Research

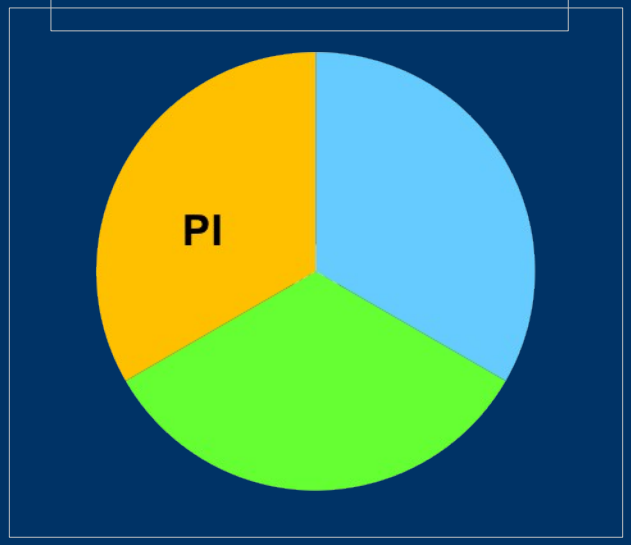
Properties of DAAs of Clinical Importance



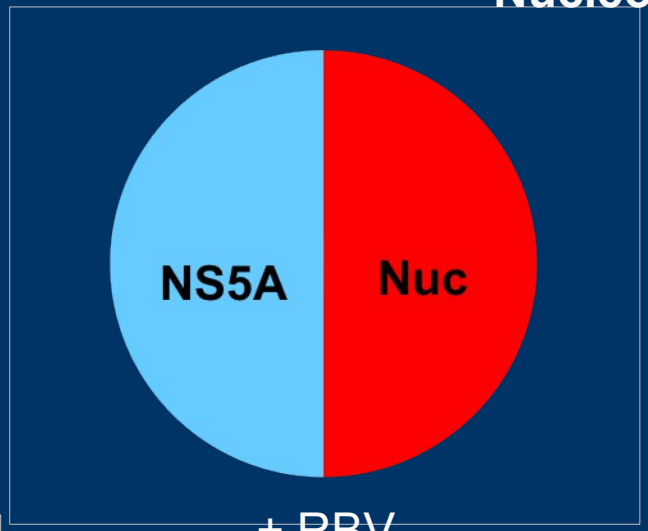
Highly Effective DAA Regimens for Genotype 1a/b

No nucleotide

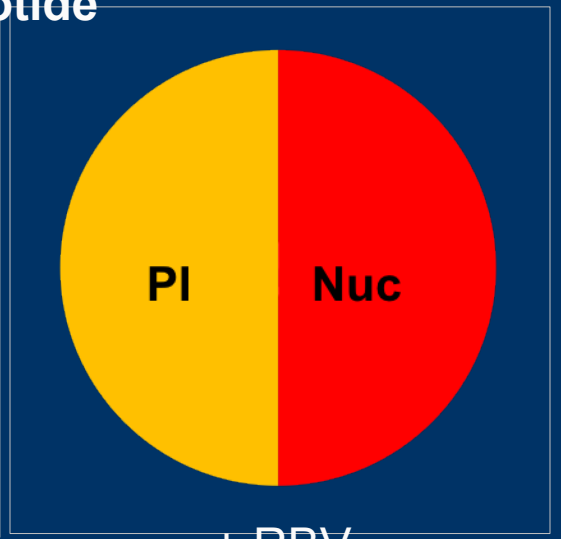




Nucleotide



± RBV



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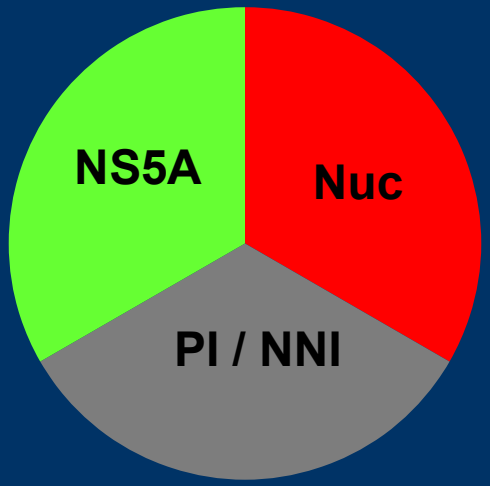
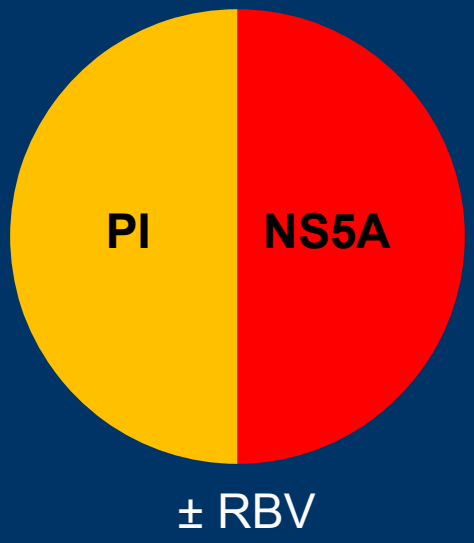


Abbreviations: NNI, nonnucleoside inhibitor; NS5A, nucleoside 5A inhibitor; Nuc, nucleotide; PI, protease inhibitor; RBV, ribavirin.

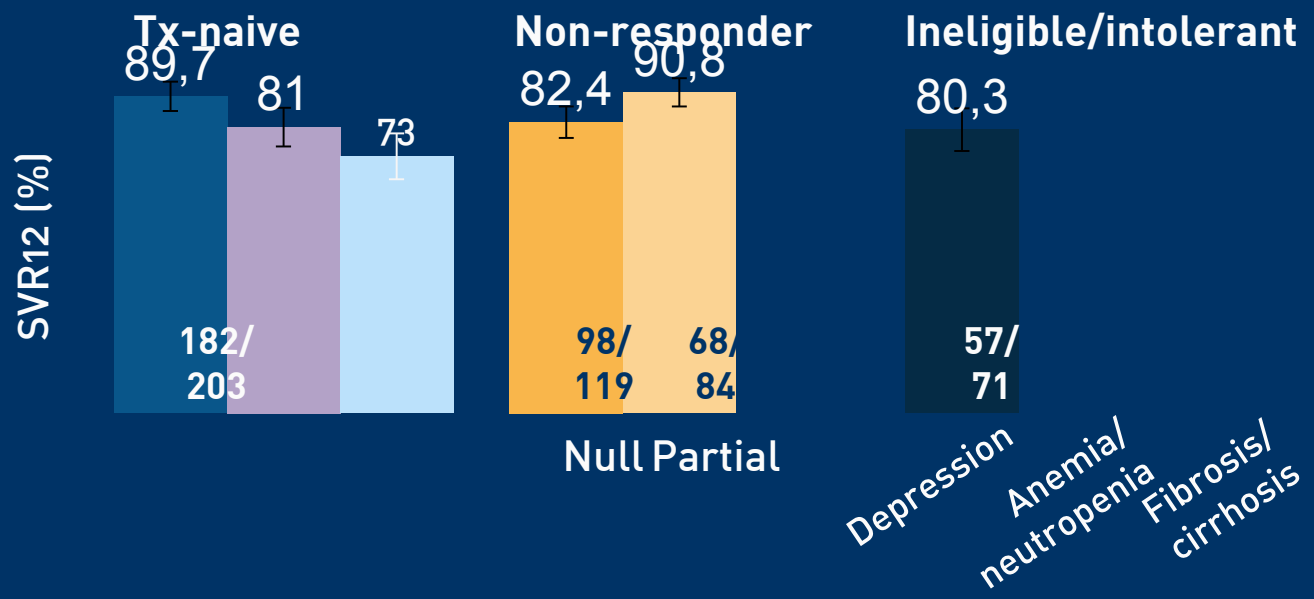
Less Effective DAA Regimens focus on Genotype 1b only

No nucleotide



Outcomes

Hallmark Study
Asunaprevir / Daclatasvir



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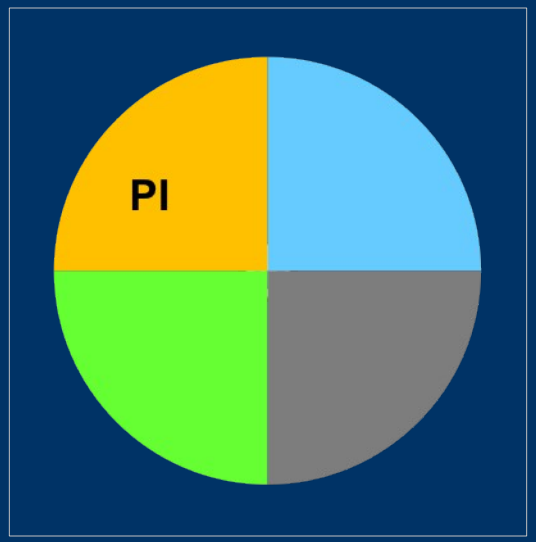
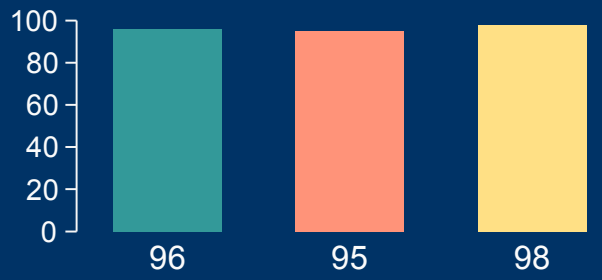


R – ABT450
Ombitasvir
Dasabuvir
Ribavirin

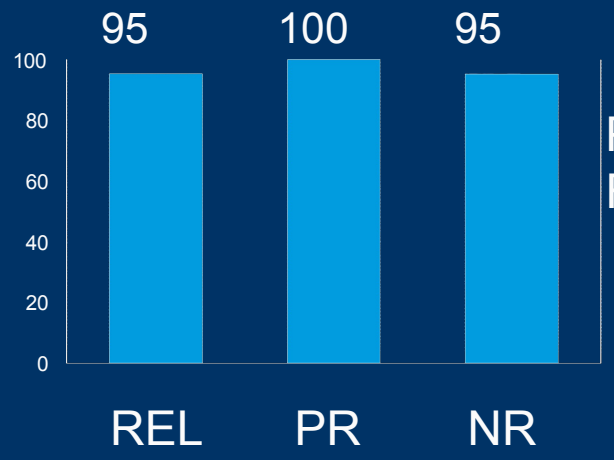
Outcomes and Regimens

% SVR AbbVie 3D regimen



NAIVE

PEG/RBV Failure



PEG/RBV Failure

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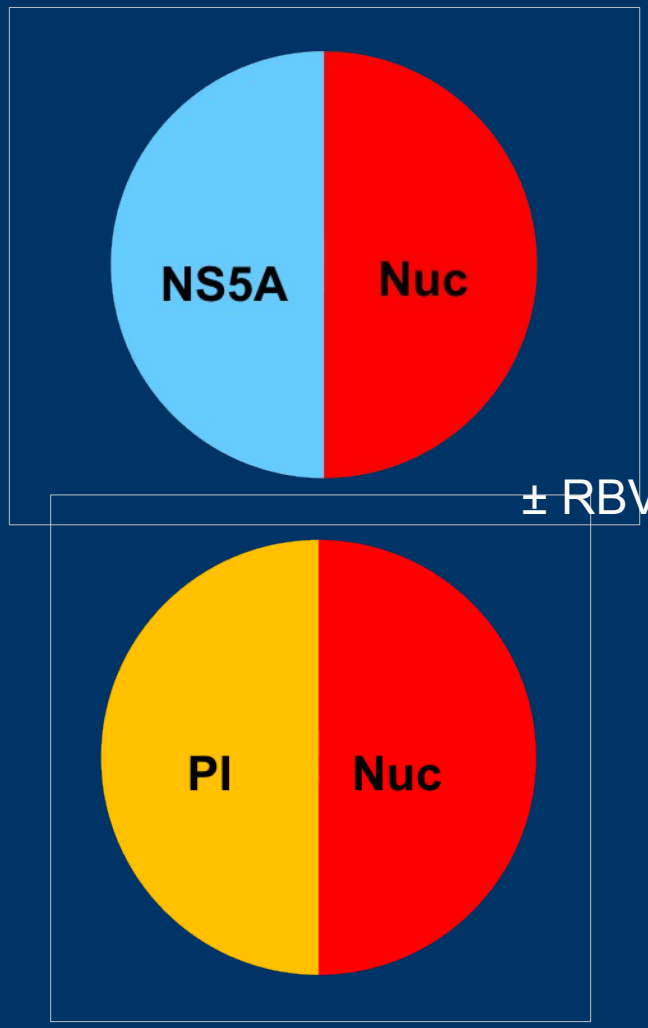
Highly Effective DAA Regimens for Genotype 1a/b

Nucleotide Backbone Treatment



ION TRIALS
SOF / LED
8, 12 and 24 weeks

SVR 94 – 100%

COSMOS TRIAL
SOF / SIM
12 and 24 weeks

SVR 95%

Abbreviations: NNI, nonnucleoside inhibitor; NS5A, nucleoside 5A inhibitor; Nuc, nucleotide; PI, protease inhibitor; RBV, ribavirin.

Treatment of HCV Special Populations

	REGIMEN / SVR
• Cirrhosis 85 – 99% SOF-LED	AbbVie 3D /
• Pre-transplant	SOF/RBV 70%
• Childs B / C	SOF-LED 90%
• Post-Transplant	SOF-LED 90%
• PI Failures	SOF-LED 94%

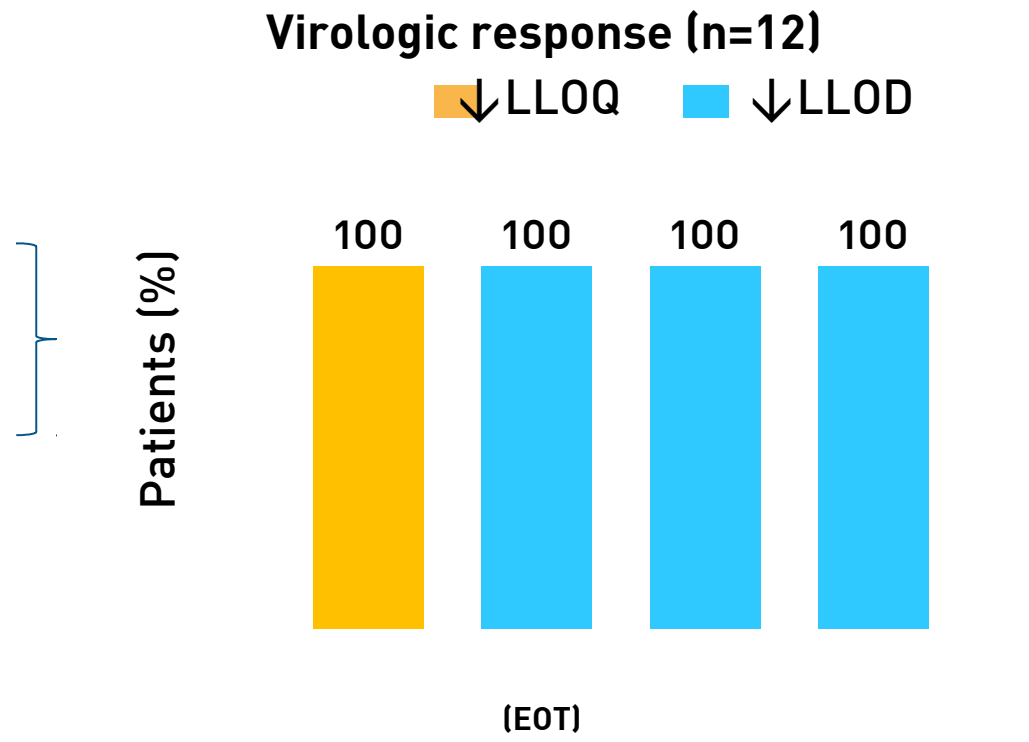
- Renal Disease remains only major subgroup needing study
- Clinical Outcomes needed in advanced liver disease patients

Shortening Treatment Duration

- Convenience
- Compliance
- Cost

- Cannot sacrifice SVR
- Must be predictable for different patient populations – kinetic / immunological predictors
- Must have a real clinical rationale

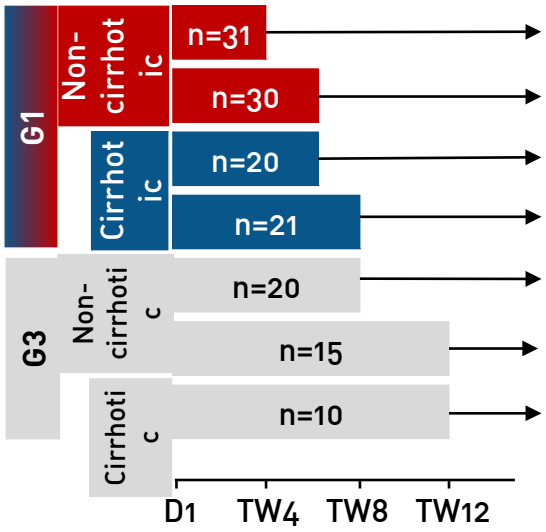
treatment with ACH-3102 and SOF in G1 treatment-naive patients: A Phase 2 'proxy' study



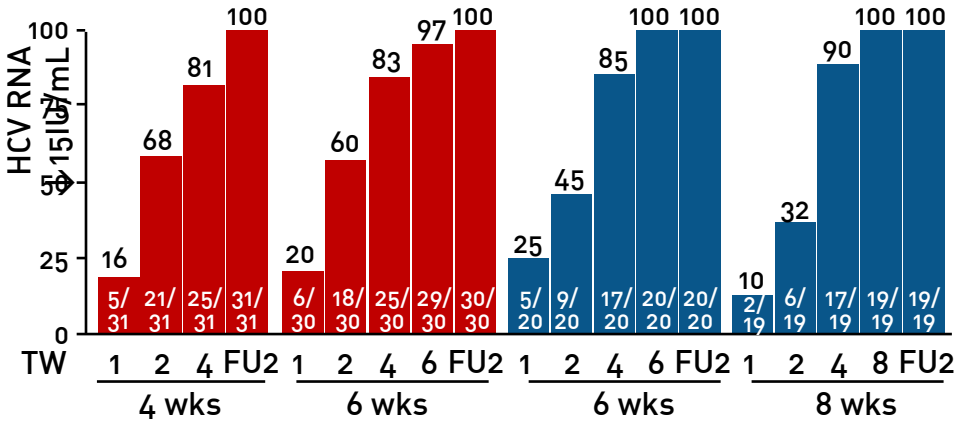
Promising clinical results consistent with preclinical profiles of both drugs

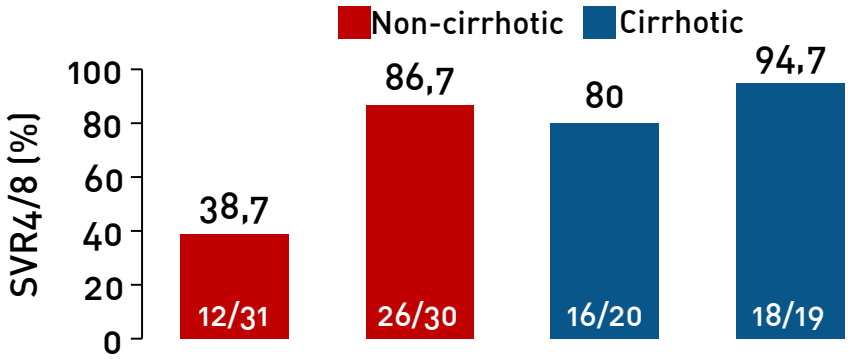
Potential in long-term for new combinations of NS5A/nucleotide ± other DAA to enter the HCV treatment space

C-SWIFT: MK-5172 (grazoprevir)+ MK-8742 (elbasvir) + SOF in treatment-naive G1 pts with/without cirrhosis, for 4, 6, or 8 weeks



Primary endpoint : SVR12





Breakthrough	**0**	**0**	**0**	**0**
Relapse				
All relapse	**19**	**4**	**4**	**1**
Relapse at FU4	**10**	**4**	**2**	**1**
Relapse at FU8	**9**	**0**	**2**	**0**

C-SWIFT: MK-5172 (grazoprevir)+ MK-8742 (elbasvir) + SOF in treatment-naive G1 pts with/without cirrhosis, for 4, 6, or 8 weeks

International Hepatitis Education Program

8 pts with BL NS5A RAVs:

Tx group	BL NS5A RAV, n	SVR in pts with NS5A RAVs, n (%)	No BL NS5A RAV, n	SVR in pts with no NS5A RAVs, n (%)
4-wk	3	0 (0)	28	12 (43)
6-wk	3	2 (66)	47	40 (85)
8-wk	2	1 (50)	17	17 (100)
Total	**8**	**3 (38)**	**92**	**69 (75)**

- 3 pts from 4-wk Tx: 3 VFs
- 3 pts from 6-wk Tx: 2 SVR, 1 VF
- 2 pts from 8-wk Tx: 1 SVR, 1 VF

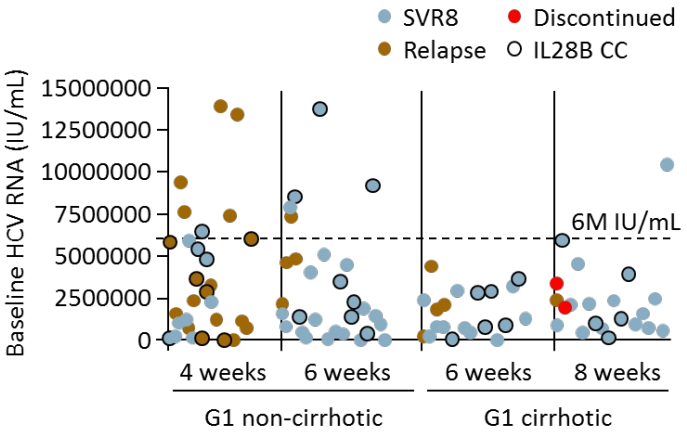
- NS3 BL RAV: 1 pt (this pt achieved SVR)
- NS5B BL RAV: None

First trial to cure patients with designed 4-wk duration but reaches limits of biologic plausibility with current generation of antivirals as high relapse seen

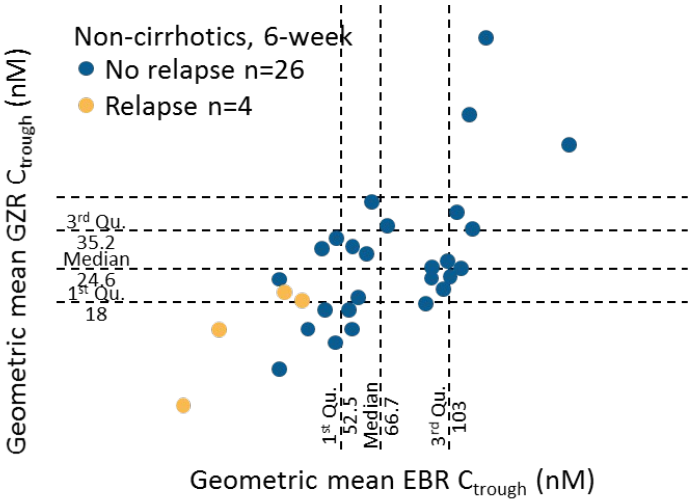
High viral load and non CC predictive of failure with

4-week duration

Impact of BL HCV RNA and IL28CC on SVR4/8



Pharmacokinetics: Non-cirrhotic G1 pts (6-week) Grazoprevir/elbasvir Ctrough



Phase 1/2a study assessing 7-day dosing of MK-3682 (formerly IDX21437) in HCV-infected subjects

International Hepatitis Education Program

MK-3682 is a uridine nucleotide polymerase inhibitor

N*	Genotype	Dose	Study drug administration
8:2	1	50 mg	MK-3682 or PBO QD x 7 days
8:2 *Active:PBO	1	150 mg	MK-3682 or PBO QD x 7 days
8:2	1	300 mg	MK-3682 or PBO QD x 7 days

N (G2/3)	Dose	Drug administration
0/5	50 mg	MK-3682 QD x 7 days
1/4	150 mg	MK-3682 QD x 7 days
3/7	300 mg	MK-3682 QD x 7 days

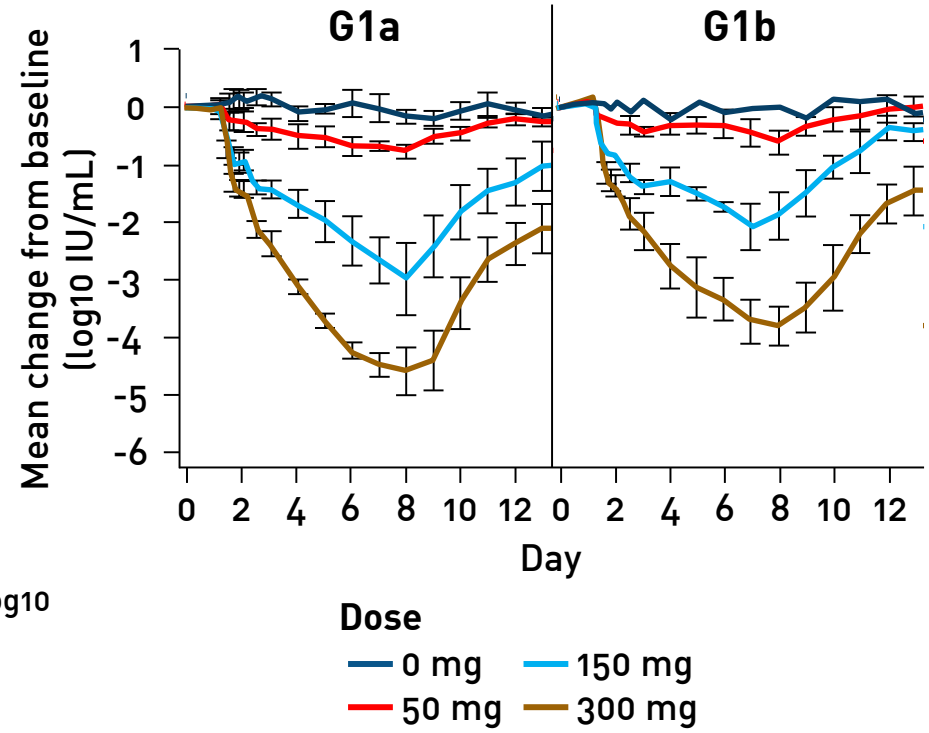
G1

Mean maximum HCV RNA reduction †	PBO QD x7 days (n=5)	MK-3682 dose x 7 days		
		50 mg QD (n=6)	150 mg QD (n=5)	300 mg QD (n=8)
Mean (SE)	0.31 (0.102)	0.74 (0.081)	2.61 (0.431)	4.23 (0.277)
Median	0.36	0.78	2.46	4.29
SD	0.227	0.197	0.964	0.782
25%, 75%	0.20, 0.44	0.63, 0.90	1.98, 2.84	3.57, 4.82
Min, Max	-0.02, 0.57	0.42, 0.96	1.65, 4.43	3.12, 5.36

log10 IU/mL

G1a n=3 4.8 log10

G1b n=5 3.9 log10



Gane EJ, et al. AASLD 2014, Boston. #1974

Phase 1/2a study assessing 7-day dosing of MK-3682 (formerly IDX21437) in HCV-infected subjects

International Hepatitis Education Program

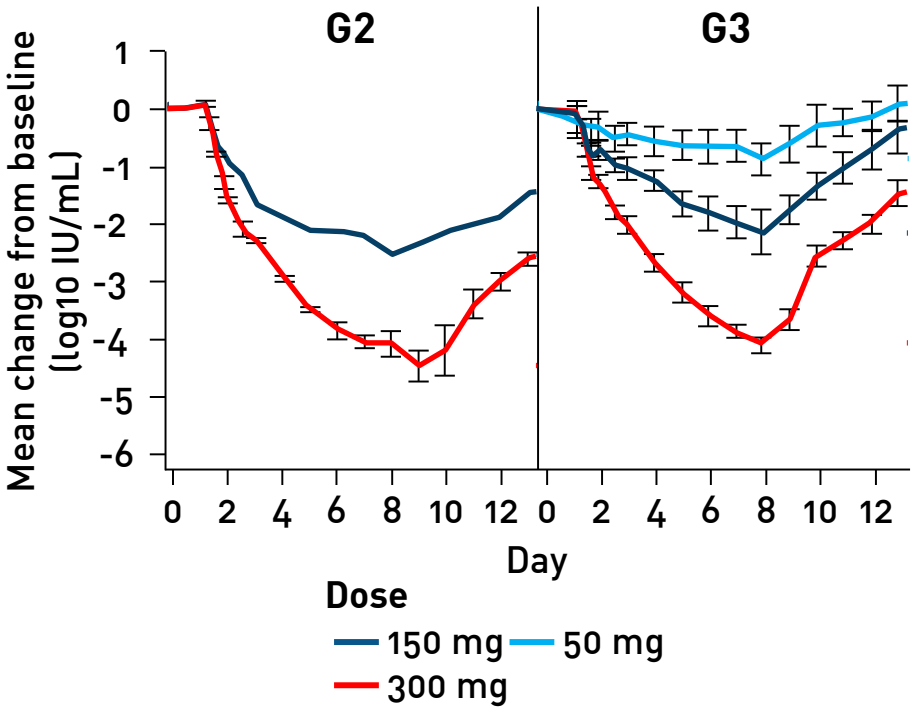
G2/3

Mean maximum HCV RNA reduction†	MK-3682 dose x7 days		
	50 mg QD (n=5)	150 mg QD (n=5)	300 mg QD (n=10)
Mean (SE)	1.01 (0.279)	2.24 (0.308)	4.27 (0.144)
Median	1.14	2.09	4.12
SD	0.624	0.688	0.454
25%, 75%	1.00, 1.42	1.76, 2.51	3.93, 4.78
Min, Max	-0.03, 1.54	1.55, 3.29	3.68, 5.03

†log10 IU/mL

G2 n=3 4.6 log

G3 n=7 4.1 log



New uridine nucleotide polymerase inhibitor achieves potent activity (↑4 logs)
in G1–3 at 300 mg
No safety signals to date; await safety and efficacy data from longer exposures

Pangenotypic all oral regimen: Sofosbuvir/GS-5816

Picomolar activity
in GT 1-6

High SVR rates in Phase 2 studies

- 12-week treatment
- No RBV

Phase 3 program underway