Efficacy and Safety of Daclatasvir in Combination With Asunaprevir in Cirrhotic and Non-Cirrhotic Patients With HCV Genotype 1b: Results of the HALLMARK-DUAL Study

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Background

- Current treatment of chronic HCV infection in patients with cirrhosis is complicated by poor tolerability and suboptimal sustained virologic response (SVR) rates with peginterferon/ribavirin (pegIFN/RBV) alone or in combination with direct-acting antivirals[1-3]
- Thus, there is a high unmet medical need for IFN- and RBV-free treatments for patients with cirrhosis
- In a phase 3 Japanese study in genotype (GT) 1b (AI447-026), all-oral daclatasvir (DCV) plus asunaprevir (ASV) demonstrated high SVR_{24} rates in IFN non-responders and ineligible-naive/intolerant patients with and without cirrhosis (91% and 84%, respectively)[4]

1. Bourlière M, *et al. Liver Int* 2012;32(Suppl 1):113-119.
2. Lawitz E, *et al. N Engl J Med* 2013;368:1878-1887.
3. OLYSIO™ (simeprevir) prescribing information. Food and Drug Administration. 2014. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001lbl.pdf.)
4. Kumada H, *et al. Hepatology* 2014 (ePub). doi:10.1002/hep.27113.
5. Manns M *et al. 49th EASL*; Apr 9-13, 2014; London, United Kingdom. Late Breakers oral 0166.

Background

- DCV + ASV was evaluated in a global phase 3 study in patients with GT 1b who were treatment-naive, non-responders to peg-IFN/RBV, or peg-IFN/RBV ineligible/intolerant
  - Daclatasvir (DCV)
    - Potent, pangenotypic[a] NS5A inhibitor
    - Once daily with low potential for drug-drug interactions[b]
    - Safe and well tolerated in > 5500 patients treated
  - Asunaprevir (ASV)
    - NS3 protease inhibitor
    - Clinical data in GT 1 and 4
    - Generally well tolerated in > 2000 patients treated
- Primary efficacy and safety results (including data on resistance) from this study were presented at EASL 2014[5]
- Efficacy and safety results in patients with and without cirrhosis are presented here

[a] Pangenotypic: GT 1-6 *in vitro* and GT 1-4 in clinical trials.
[b] No clinically significant drug-drug interactions with anti-retrovirals and transplant medications.

1. Bourlière M, *et al. Liver Int* 2012;32(Suppl 1):113-119.
2. Lawitz E, *et al. N Engl J Med* 2013;368:1878-1887.
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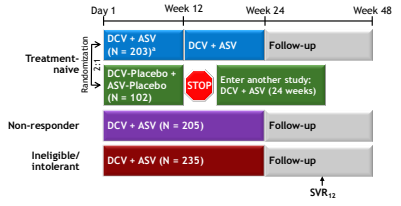
Methods

Study Design

- This global phase 3 study evaluated DCV (60-mg tablet once daily) combined with ASV (100-mg softgel capsule twice daily) in patients with GT 1b

Figure 1. HALLMARK-DUAL Study (AI447-028) Design



[a] Excludes 2 patients inadvertently assigned, instead of randomized, to DCV + ASV; patients were excluded from efficacy analyses but both achieved SVR_{12}.

Patient Eligibility Criteria

- Patients: men and women aged ≥ 18 years
- Treatment-naive
- Prior peg-IFN/RBV non-responders (null or partial response)
- Peg-IFN/RBV ineligible/intolerant (treatment-naive or -experienced)
  - Depression
  - Anaemia/neutropenia
  - Compensated advanced fibrosis/cirrhosis (F3/F4) with thrombocytopenia (screening platelets 50 to < 90 x 10^9 cells/L and/or history of thrombocytopenia on peg-IFN/RBV)
- Primary endpoint: proportion of DCV + ASV-treated patients with SVR_{12}
- Efficacy and safety with DCV + ASV were assessed in patients with and without cirrhosis
- Presence of cirrhosis assessed by liver biopsy or transient elastography (FibroScan; ≥ 14.6 kPa)

Results

Demographics & Baseline Disease Characteristics

Parameter	Cirrhotic (N = 223)	Non-cirrhotic (N = 524)
Age, median years	59	56
Male, n (%)	121 (54)	243 (46)
Race, n (%)		
White	153 (69)	358 (68)
Black	8 (4)	34 (6)
Asian	60 (27)	126 (24)
Other[a]	2 (1)	6 (1)
HCV RNA, n (%)		
< 800,000 log_{10} IU/mL	48 (22)	106 (20)
≥ 800,000 log_{10} IU/mL	175 (78)	418 (80)
IL28B genotype, n (%)		
CC	65 (33)	122 (28)
Non-CC	132 (67)	317 (72)
Prior treatment experience, n (%)		
Treatment naive[b]	49 (22)	258 (49)
Nonresponder	63 (28)	142 (27)
Ineligible/intolerant[c]	111 (50)	124 (24)

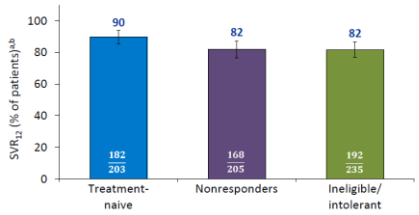
[a] Includes North African, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, and Other (Afghanistan [Middle East], mixed, southwest Asian).

[b] Cirrhotic: 33 DCV + ASV, 16 placebo; non-cirrhotic: 172 DCV + ASV, 86 placebo.

[c] Prior anti-HCV treatment taken by 182/235 (77%) patients.

- Baseline characteristics were comparable in cirrhotic and non-cirrhotic patients
- 90% of cirrhotic patients and 89% of non-cirrhotic patients completed DCV + ASV treatment

Primary Endpoint: Virologic Response SVR_{12}



- SVR_{12} rates documented on or after post-treatment Week 12[5,a]
  - Treatment-naive: 91%
  - Non-responders: 82%
  - Ineligible/intolerant: 83%

[a] HCV RNA < lower limit of assay quantitation (25 IU/mL). [b] Patients with missing SVR12 data counted as treatment failures.
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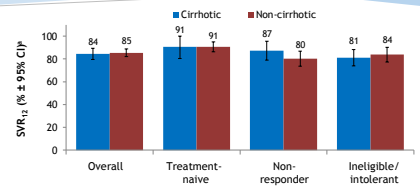
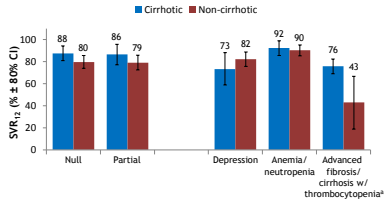
Virologic Response by Cirrhosis Status



- SVR_{12} was achieved in a similar proportion of cirrhotic and non-cirrhotic patients
- When patients with missing SVR_{12} data were counted as treatment failures, rates were identical except for treatment-naive non-cirrhotic patients (89%) and ineligible/intolerant cirrhotic patients (79%)
- 69% of cirrhotic patients and 76% of non-cirrhotic patients had undetectable HCV RNA at on-treatment Week 4

[a] SVR_{12} documented on or after post-treatment Week 12.

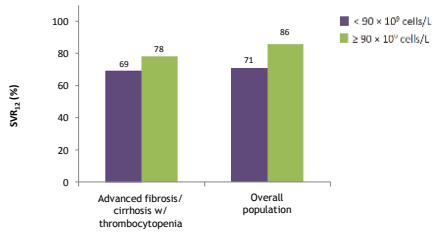
Virologic Response in Cirrhotics & Non-Cirrhotics by Patient Subgroup



[a] The 7 non-cirrhotic patients includes 6 with advanced fibrosis (F3) and 1 not reported.

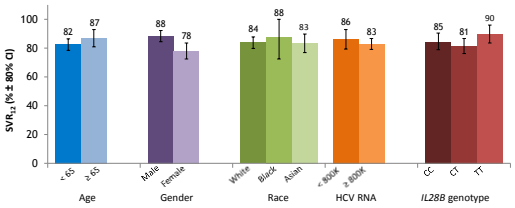
- Patients with cirrhosis achieved high SVR_{12} rates across all subgroups
- Among ineligible/intolerant patients, SVR_{12} rate was slightly lower in those with advanced fibrosis/cirrhosis with thrombocytopenia (73%) versus depression (80%) and anaemia/neutropenia (91%)

Virologic Response by Baseline Platelet Count



- In the subgroup with advanced fibrosis/cirrhosis with thrombocytopenia, SVR_{12} rates were lower in patients with baseline platelet counts < 90 versus ≥ 90 x 10^9 cells/L
  - Similar results seen in the overall patient population

Virologic Response in Cirrhotics by Baseline Factors



- Cirrhotic and non-cirrhotic patients had similar virologic responses based on baseline factors

Patients Without SVR_{12} by Cirrhosis Status

Patients, n (%)	Cirrhotic (N = 206)	Non-cirrhotic (N = 437)
All	34 (17)	67 (15)
On-treatment failures		
Virologic breakthrough	16 (8)	39 (9)
Detectable or missing RNA at end of treatment	8 (4)	8 (2)
Posttreatment failures		
Relapse[a]	8 (5)	16 (4)
Missing RNA at posttreatment Week 12[a]	2 (1)	4 (1)

[a] Percentages based on number of patients with undetectable HCV RNA at end of treatment (cirrhotic, n = 175; non-cirrhotic, n = 373).

- Similar proportions of cirrhotic and non-cirrhotic patients did not achieve SVR_{12}
- 14 of 28 cirrhotic patients with baseline NS5A L31 and/or Y93 resistance-associated variants achieved SVR_{12}[a]

[a] Data on resistance in overall study reported at EASL 2014.[1]

1. Manns M *et al. 49th EASL*; Apr 9-13, 2014; London, United Kingdom. Late Breakers oral 0166.

On-Treatment Safety and Tolerability by Cirrhosis Status

Patients, n (%)	Cirrhotic (N = 207)[a]	Non-cirrhotic (N = 438)[a]
Death	0	0
Serious AEs	13 (6)	26 (6)
AEs leading to discontinuation[b]	1 (0.5)	9 (2)
Common AEs (≥ 10% of patients)		
Headache	51 (25)	108 (25)
Fatigue	42 (20)	98 (22)
Diarrhea	32 (15)	71 (16)
Nausea	22 (11)	53 (12)
Grade 3/4 laboratory abnormalities		
Hemoglobin (< 90 g/L or decrease ≥ 45 g/L)	1 (0.5)	0
Absolute neutrophils (< 0.75 x 10^9 cells/L)	6 (3)	3 (1)
Lymphocytes (< 0.5 x 10^9 cells/L)	5 (2)	3 (1)
Platelets (< 50 x 10^9 cells/L)	9 (4)	2 (0.5)
ALT (> 5 x ULN)	3 (1)	12 (3)
AST (> 5 x ULN)	3 (1)	9 (2)
Total bilirubin (> 2.5 x ULN)	2 (1)	1 (0.2)

AE - adverse event
ALT - alanine aminotransferase
ULN - upper limit of normal
AST - aspartate aminotransferase

[a] Includes DCV + ASV-treated patients only.

[b] Most commonly ALT/AST elevations, which resolved off-treatment (7 patients; 6/7 including patient with cirrhosis achieved SVR_{12}).

- DCV + ASV was well tolerated in patients with cirrhosis, with no clinically meaningful differences in safety parameters in cirrhotic versus non-cirrhotic patients
- Comparison of DCV + ASV versus placebo in the initial 12 weeks in treatment-naive patients with cirrhosis showed no serious adverse events, adverse events leading to discontinuation, or grade 3/4 hematologic abnormalities or aminotransferase/total bilirubin elevations with either treatment

Conclusions

- In this global, phase 3 study with a high proportion of cirrhotic patients (≈30%), all-oral DCV + ASV achieved high SVR_{12} rates (documented on or after post-treatment Week 12)
  - SVR_{12} achieved in 84% and 85% of cirrhotic and non-cirrhotic GT 1b patients, respectively
  - In cirrhotic patients, SVR_{12} rates were 91% in treatment-naive, 87% in non-responder, and 81% in IFN-ineligible/intolerant groups
- DCV + ASV was generally well tolerated
  - No clinically meaningful differences between cirrhotic and non-cirrhotic patients in safety parameters
- DCV is being further evaluated in all-oral combination regimens in multiple patient populations of high unmet need

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