ONLINE EXPERT POSTER REVIEW AND DISCUSSION

Advances in Chronic Hepatitis C Management and Treatment

Reporting From

THE 62ND AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES ANNUAL MEETING

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Dual Oral Combination Therapy with the NS5A Inhibitor Daclatasvir (DCV; BMS-790052) and the NS3 Protease Inhibitor Asunaprevir (ASV; BMS-650032) Achieved 90% Sustained Virologic Response (SVR12) in Japanese HCV Genotype 1b-Infected Null Responders

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Abstract LB-4

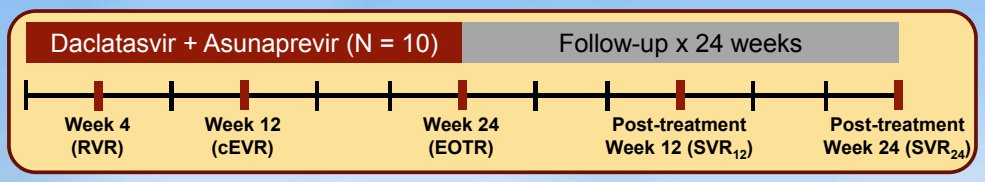
Background

- Patients with prior null response to peg-alfa/RBV frequently fail to respond to retreatment with peg-alfa/RBV alone or combined with telaprevir or boceprevier[1-4]
  - Null response: HCV RNA reduced by ≤ 2 $\log_{10}$IU/mL with ≥ 12 weeks of peg-alfa/RBV
- Daclatasvir (DCV; BMS-790052) first-in-class, once-daily, highly selective HCV NS5A replication complex inhibitor with picomolar antiviral potency and broad coverage of HCV genotypes *in vitro*[5]
- Asunaprevir (ASV; BMS-650032): selective inhibitor of the HCV NS3 protease with antiviral activity *in vitro* against HCV genotypes 1 and 4[6,7]
- High rates of SVR_{24} with daclatasvir + asunaprevir in USA null responders both as dual direct-acting antiviral (DAA) regimen (genotype 1b) and combined with peg-alfa/RBV (genotype 1a)[8]

peg-alfa/RBV, peginterferon alfa + ribavirin; SVR, sustained virologic response.

1. PoynardT, *et al. Gastroenterology* 2009; 136: 1618 – 1628;
2. Jensen DM, *et al. Ann Intern Med* 2009; 150: 528 – 540;
3. Zeuzem S, *et al. N Engl J Med* 2011; 364: 2417 – 2428;
4. Bacon BR, *et al. N Engl J Med* 2011; 364: 1207 – 1217;
5. GaoM, *et al. Nature* 2010; 425: 96 – 100;
6. McPhee F, *et al. J Hepatol* 2010; 52(suppl1): S296;
7. BronowickiJP, *et al. J Hepatol* 2011; 54(suppl1): S472;
8. Lok a, *et al. J Hepatol* 2011; 54(suppl1): S536.

Ongoing, Open-Label Phase 2a Study Sentinel Cohort, Study A1447-017



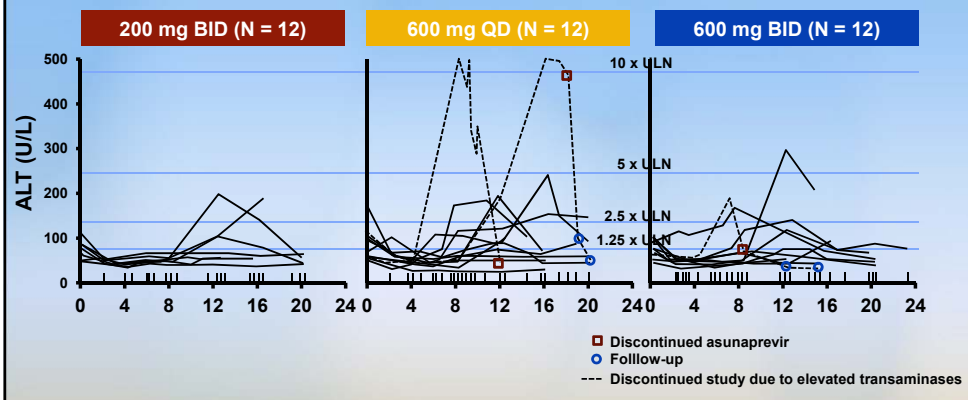
- Non-cirrhotic Japanese adults with HCV genotype 1 infection, HCV RNA >10^5 IU/mL, and prior null response to pegIFN/RBV
- Primary efficacy endpoint: undetectable HCV RNA 12 weeks post-treatment (SVR_{12})
  - Secondary: Undetectable HCV RNA at week 4 (RVR), week 12 (cEVR), weeks 4 + 12 (eRVR), end of treatment (week 24; EOTR) and at 24 weeks post-treatment (SVR_{24})
- Dual oral treatment with daclatasvir and asunaprevir for 24 weeks
  - Daclatasvir 60 mg once-daily
  - Asunaprevir initially 600 mg twice-daily, subsequently reduced to 200 mg twice daily due to elevated transaminases at 600 mg in a concurrent dose-ranging study[1]

ClinicalTrials.gov identifier NCT01051414.
cEVR, complete early virologic response; EOTR, end of treatment response; eRVR, extended rapid virologic response; IFN, interferon; RVR, rapid virologic repsonse.

1. Bronowicki JP, et al. J Hepatol 2011; 54(suppl 1): S472.

Chayama K, et al. 62nd AASLD; San Francisco, CA; November 04-08, 2011. Abst. LB-4.

Dose-related Transaminase Elevations in Phase 2a Asunaprevir Dose Ranging Study

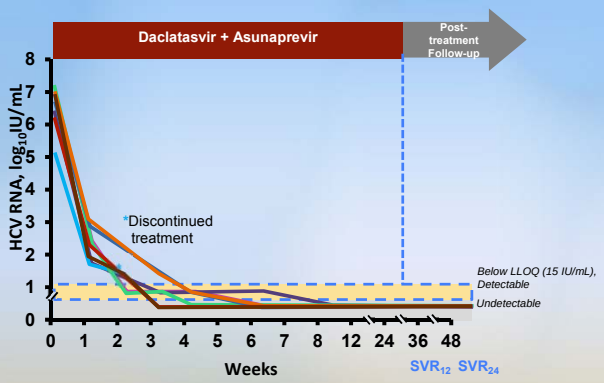


- 3 discontinued due to transaminase elevations with asunaprevir 600 mg BID or QD
- No grade 3 or 4 transaminase or bilirubin elevations with asunaprevir 200 mg BID, and no discontinuations due to hepatic adverse events
- Similar antiviral efficacy observed across all treatment groups

Bronowicki JP et al, EASL 2011. Poster 1195

Chayama K, et al. 62nd AASLD; San Francisco, CA; November 04-08, 2011. Abst. LB-4.

HCV RNA: Individual Patients (N=10)



Parameter	Daclatasvir + Asunaprevir (N = 10)
Age, median years (range)	62 (52-70)
Male, %	40
HCV genotype 1b, %	100
IL288 rs12979860 genotype, % CT CC	 80 20
HCV RNA, mean log_{10}IU/mL (SD)	6.8 (0.61)
ALT, mean U/L (SD)	60.6 (32.9)

HCV RNA determined by Roche COBAS TaqMan HCV Auto assay (Roche Diagnostics KK, Tokyo, Japan), lower limit of quantitation (LLOQ = 15 IU/mL

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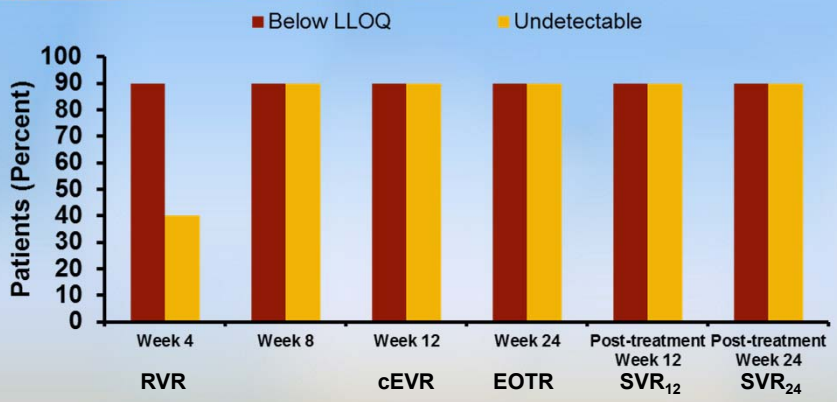
Virologic Response During and After Treatment



- One patient discontinued at Week 2; HCV RNA was undetectable after 24 weeks' follow-up

Intention to treat (missing = failure) analysis
LLOQ lower limit of quantification (15 IU/mL)

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Baseline Resistance Substitutions

Patient	NS5A[a]						NS3[b]	
	L28	R30	L31	Q54	P58	Y93	T54	Q80
1				H/Q		H/Y	S	L
2								L
3				H				
4		Q						
5			M/L					
6					T			
7								
8				H				L
9				H		H/Y		
10	M	Q						

- No apparent association between detection of baseline variants and virologic outcome

[a]Polymorphisms at amino acid positions associated with resistance to daclatasvir
[b]Polymorphisms associated with low-level resistance to telaprevir, boceprevir, and/or TMC435

1. Fridell Ra, et al. AntimicrobAgents Chemother 2010; 54: 3641 – 3650;
2. Romano KP, et al. ProcNatlAcadSciUSA 2010; 107: 20986 – 20991.

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Adverse Events Through End of Treatment

- Serious adverse events occurred in two patients
  - Grade 3 pyrexia
  - Grade 4 hyperbilirubinemia; treatment discontinued at week 2
- No other grade 3 or 4 adverse events in patients who completed 24 weeks
- No deaths
- No clinically relevant changes in electrocardiogram parameters
- Transaminase elevations
  - Mild (grade 1) and transient ALT elevations in two patients
  - One moderate (grade 2) elevation commencing week 16 through end of treatment, normalized within two weeks post-treatment

Number of On-Treatment Adverse Events Occurring in ≥ 2 Patients

Event type	Daclatasvir + Asunaprevir (N = 10)
Diarrhea	7
Headache	4
ALT increase	3
AST increase	3
Lymphopenia	2
Abdominal discomfort	2
Malaise	2
Pyrexia	2
Nasapharyngitis	2
Lipase increase	2
Back pain	2

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Patient Discontinuation

- Female aged 60, hospitalized with infectious gastroenteritis, discontinued at week 2 for hyperbilirubinemia
- Hyperbilirubinemia, but not gastroenteritis, considered by investigator to be related to study drug
  - Cefotiam and/or merpenem may have conributed to elevated bilirubin[1,2]
- HCV RNA 1.8 $\log_{10}$IU/mL at discontinuation
  - Undetectable 2 weeks later
  - Undetectable through 24 weeks of post-treatment follow-up (SVR_{24})

Day 1: Initiates study medication

Day 10: Develops diarrhea

Day 11: Cefotiam initiated

Day 14: Hospitalized with fever and vomiting
- Diagnosis of gastroenteritis
- Merpenem administered

Day 16: Study medication discontinued
- Bilirubin 7.7 mg/dL
- Normal ALT, AST and AP

Days 30-35: Grade 4 ALT/AST and grade 3 lipase elevations hyperbilirubinemia resolving

Week 7: Event considered resolved
- ALT, AST, bilirubin near normal
- HCV RNA remains undetecable

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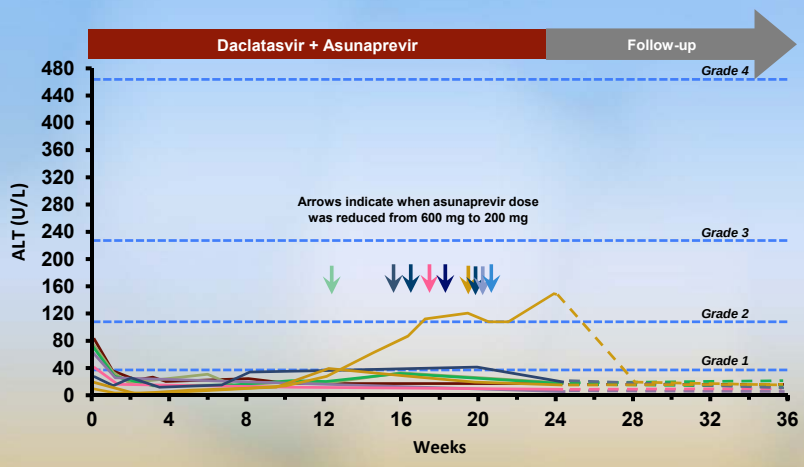
ALT Levels by Patient and Visit



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Conclusions

- Dual oral therapy with daclatasvir and asunaprevir provided rapid and persistent viral suppression in null responders with genotype 1b infection
  - All patients who completed 24 weeks' treatment achieved SVR_{24}
  - HCV RNA also undetectable 24 weeks post-treatment in patient who discontinued after only 2 weeks
- No apparent association between baseline resistance polymorphisms and virologic outcome
- Daclatasvir + asunaprevir combination was generally well tolerated
  - Adverse event profile compares favorably with historical experience with peg-alfa/RBV
- High cure rates are possible with dual oral DAA therapy in patients with genotype 1b infection

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