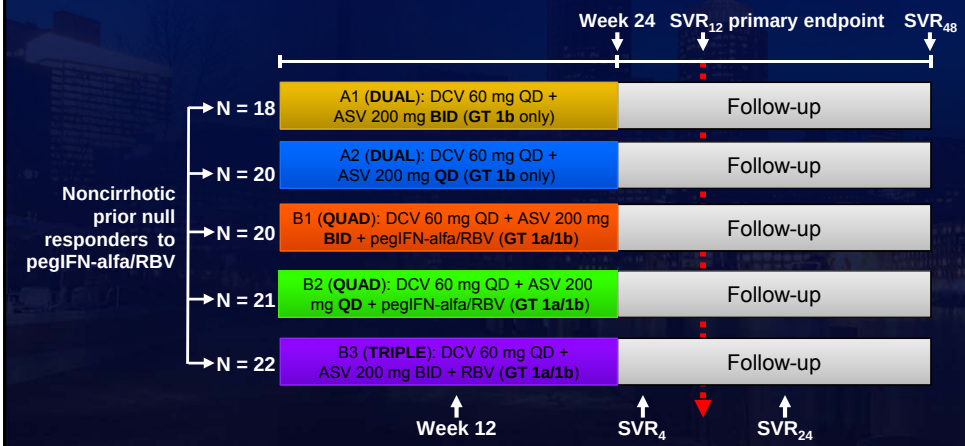
Sustained Virologic Response in Chronic HCV Genotype (GT) 1-Infected Null Responders With Combination of Daclatasvir (DCV; NS5A Inhibitor) and Asunaprevir (ASV; NS3 Inhibitor) With or Without Peginterferon Alfa-2a/Ribavirin (PEG/RBV)

Lok AS, Gardiner DF, Hézode C, Lawitz EJ, Bourlière M, Everson GT, Marcellin P, Rodriguez-Torres M, Pol S, Serfaty L, Eley T, Huang S-P, Wind-Rotolo M, McPhee F, Grasela DM, and Pasquinelli C

Abstract 79

Study AI447-011 Expansion Cohort



- HCV RNA assayed with Roche COBAS® TaqMan® HCV v2.0
  - LLOQ, 25 IU/mL; LOD, ≈ 10 IU/mL
  - Reported as < LLOQ or < LLOQ-TND (target not detected)

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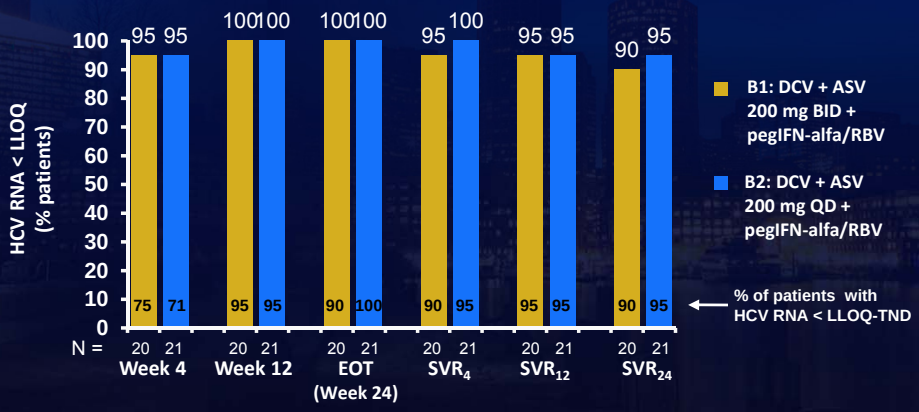
Virologic Response
QUAD Therapy: B1 and B2 (GT 1a/1b, mITT)



- No viral breakthrough
- 2 patients relapsed—1 at PT week 4 (B1); 1 at PT week 12 (B2)

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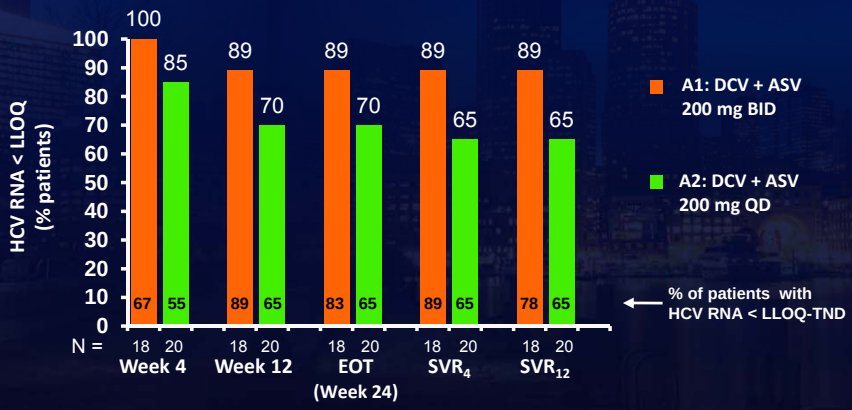
Virologic Response
DUAL Therapy: A1 and A2 (GT 1b; mITT)



- Viral breakthrough in 8 patients (A1, 2; A2, 6)—all received rescue; 1 relapse (A2) at PT Week 4
- Of 4 patients in A1 not achieving SVR12, 2 had HCV RNA < LLOQ-TND on subsequent visits

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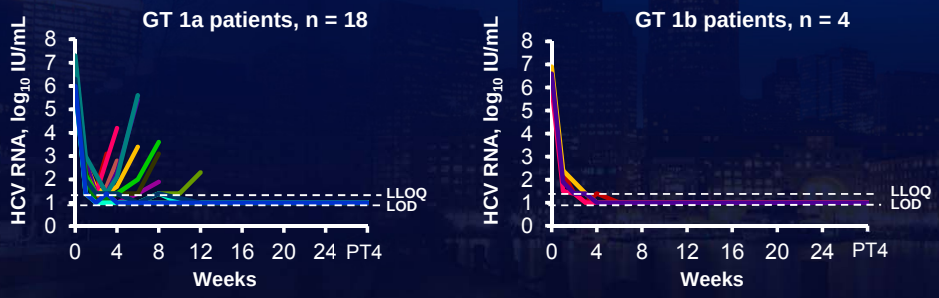
Individual HCV RNA Levels TRIPLE Therapy (B3)

DCV + ASV 200 mg BID + RBV
Graphs truncated at viral breakthrough



- 10 GT 1a patients experienced viral breakthrough
  - 7 GT 1a patients added pegIFN preemptively and continue on Quad therapy
- 1 GT 1a patient completed triple therapy and achieved SVR4

LLOQ 25 IU/mL; LOD ≈ 10 IU/mL; DCV 60 mg QD; RBV, ribavirin, 1000–1200 mg/d, weight-based.

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Conclusions

- QUAD regimen of DCV, ASV 200 mg BID or QD, and pegIFN-alfa/RBV for 24 weeks resulted in rapid and durable HCV RNA suppression, with a 95% rate of SVR_{12} and 90-95% rate of SVR_{24} in this difficult-to-treat population—mainly GT 1a, IL28B CT/TT, null responders
  - When pegIFN-alfa was omitted from the regimen (*i.e.*, TRIPLE therapy with DCV + ASV + RBV), breakthrough occurred in a high proportion (56%) of GT 1a patients while 100% (4/4) GT 1b patients achieved SVR_4
- DUAL regimen of DCV + ASV in GT 1b prior null responders
  - 78% SVR_{12} with ASV 200 mg BID
    - Two patients counted as failures had HCV RNA < LLOQ-TND at later follow-up
  - 65% SVR_{12} with ASV 200 mg QD
- DCV plus ASV with or without pegIFN-alfa/RBV was generally well tolerated
  - These data suggest that interferon-free treatment regimens for GT 1 patients may need to be tailored according to subgenotype

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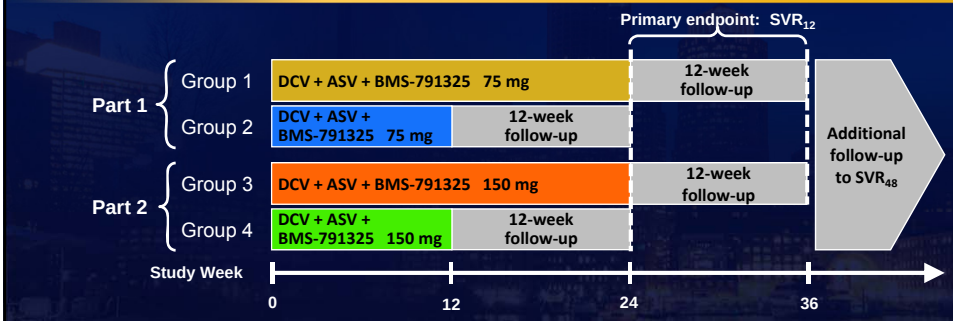
An Interferon-Free, Ribavirin-Free 12-Week Regimen of Daclatasvir (DCV), Asunaprevir (ASV), and BMS-791325 Yielded SVR4 of 94% in Treatment-Naïve Patients with Genotype (GT) 1 Chronic Hepatitis C Virus (HCV) Infection

Everson GT, Sims KD, Rodriguez-Torres M, Hézode C, Lawitz E, Bourlière M, Loustaud-Ratti V, Rustgi V, Schwartz H, Tatum H, Marcellin P, Pol S, Thuluvath PJ, Eley T, Wang X, Huang SP, McPhee F, Wind-Rotolo M, Chung E, Pasquinelli C, Grasela DM, Gardiner DF

Abstract LB-3

Phase 2a Open-Label Study (AI443-014)



- Patients: treatment-naïve, non-cirrhotic, HCV GT 1 stratified by subtype 1a/1b
- Treatment: DCV 60 mg QD + ASV 200 mg BID + BMS-791325 either 75 mg BID (Part 1) or 150 mg BID (Part 2)
- HCV RNA endpoints: per FDA guidance, HCV RNA < $LLOQ_{TD}$ = target detected but below the assay lower limit of quantitation (LLOQ; 25 IU/mL); $LLOQ_{TND}$ = below LLOQ and target not detected (previously referenced as HCV RNA undetectable or < LOD; ≈ 10 IU/mL for this study)
- Primary endpoint: HCV RNA < LLOQ 12 weeks posttreatment (SVR_{12})
  - Modified intent-to-treat analysis: missing, breakthrough, or relapse = failure
- Interim analysis: Part 1 results reported through posttreatment week 4 (Group 1; SVR_4) or posttreatment week 12 (Group 2; SVR_{12}); Part 2 enrolled and ongoing, results not yet available

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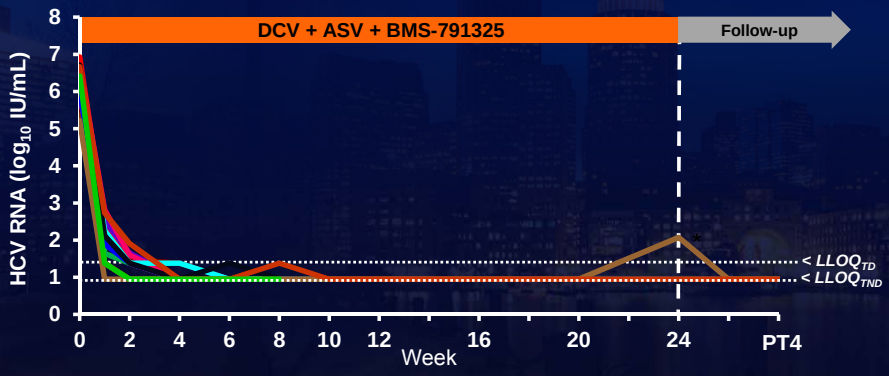
HCV RNA, Individual Patients
24-Week Treatment (Group 1)



* HCV RNA 118 IU/mL at last on-treatment visit but < LLOQTND 2 and 4 weeks posttreatment (SVR4)
< LLOQTD HCV RNA detected but below the assay lower limit of quantitation (LLOQ; 25 IU/mL)
< LLOQTND HCV RNA < LLOQ and not detected (< ≈ 10 IU/mL, previously reported as HCV RNA undetectable)
PT, posttreatment

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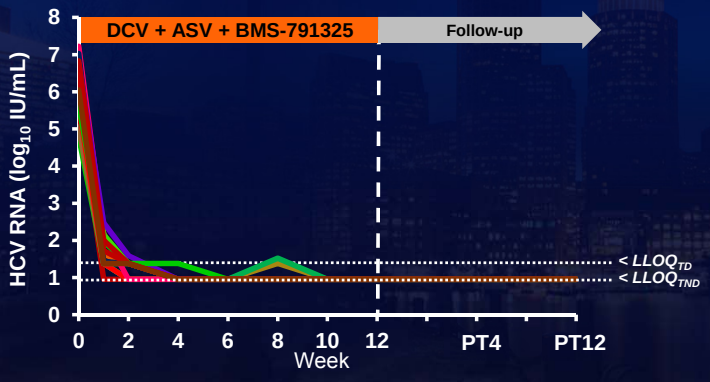
HCV RNA, Individual Patients
12-Week Treatment (Group 2)



< LLOQTD HCV RNA detected but below the assay lower limit of quantitation (LLOQ; 25 IU/mL)
< LLOQTND HCV RNA < LLOQ and not detected (< ≈ 10 IU/mL, previously reported as HCV RNA undetectable)
PT, posttreatment

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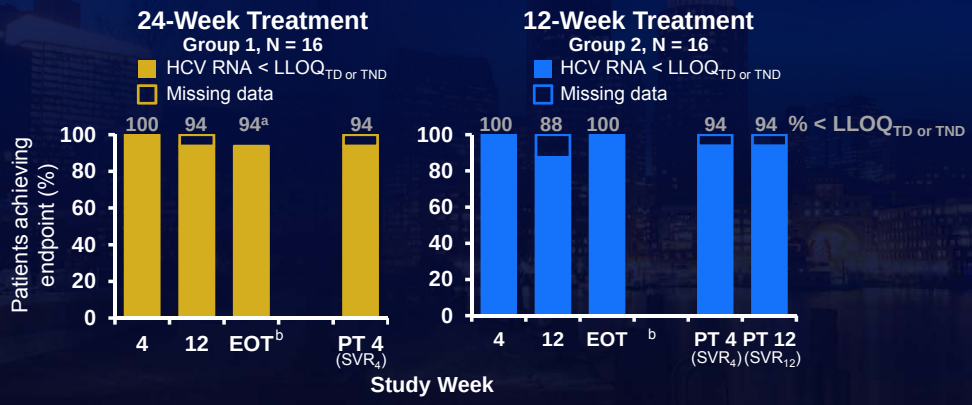
HCV RNA Endpoints

Modified Intention-to-Treat Analysis



[a] Includes 1 patient with HCV RNA 118 IU/mL at last on-treatment visit but < LLOQTND 2 and 4 weeks posttreatment (SVR4).
[b] EOT, end of treatment; includes patients who discontinued prior to the protocol-defined last treatment visit.
< LLOQTD or TND, HCV RNA below assay lower limit of quantitation (25 IU/mL) and target detected (LLOQTD) or target not detected (LLOQTND);
HCV RNA < LOD ≈ 10 IU/mL, previously reported as HCV RNA undetectable); PT, posttreatment.

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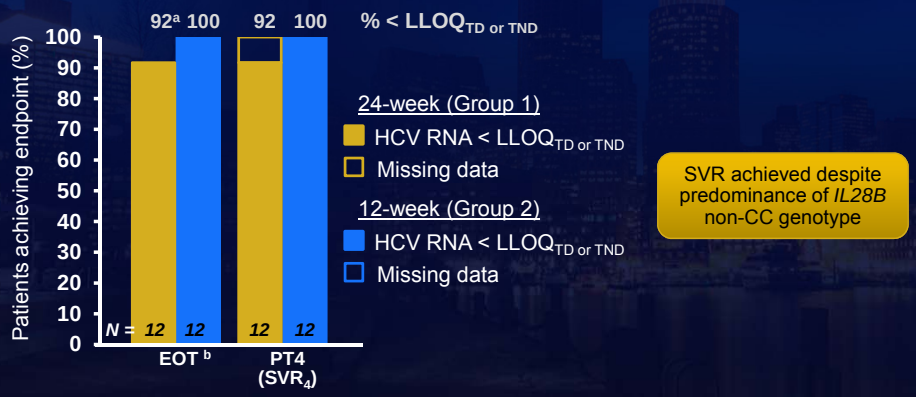
HCV RNA Outcomes – HCV Genotype 1a Subtype

Modified Intention-to-Treat Analysis



SVR achieved despite predominance of *IL28B* non-CC genotype

[a] Includes 1 patient with HCV RNA 118 IU/mL at last on-treatment visit but < LLOQTND 2 and 4 weeks posttreatment (SVR4).
[b] EOT, end of treatment; includes patients who discontinued prior to the protocol-defined last treatment visit.
< LLOQTD or TND, HCV RNA below assay lower limit of quantitation (25 IU/mL) and target detected (LLOQTD) or target not detected (LLOQTND);
HCV RNA < LOD ≈ 10 IU/mL, previously reported as HCV RNA undetectable); PT, posttreatment.

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Conclusions

- This interferon-free and ribavirin-free triple DAA combination of DCV + ASV + BMS-791325 resulted in high rates of SVR after both 12 and 24 weeks of treatment
  - SVR_4 was achieved in all treatment-naïve GT 1 patients with posttreatment data available, including harder-to-treat patients with GT 1a and IL28B non-CC genotypes
  - SVR_4 and SVR_{12} results were consistent following 12 weeks of triple DAA treatment
  - Regimen was generally well tolerated
- There was no viral breakthrough and no posttreatment relapse to date
- Further investigation of this regimen in the treatment of HCV is warranted

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