All-Oral Combination of Daclatasvir Plus Asunaprevir in Interferon-Ineligible Naive/Intolerant and Nonresponder Japanese Patients Chronically Infected With HCV Genotype 1b: Results From a Phase 3 Trial

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Background

- Current treatment for chronic HCV consists of peginterferon/RBV combined with a direct-acting antiviral
- In Japan, many patients are excluded from therapy due to the combined effect of an aging Japanese population with chronic HCV and the poor tolerability profile with peginterferon/RBV-based therapy in this population[1]
- Although telaprevir/peginterferon/RBV therapy was approved for both treatment-naïve and treatment-experienced patients, the efficacy in nonresponder patients with HCV genotype-1 was insufficient (34.4%)[2]
- Therefore, a great unmet medical need remains for a new HCV treatment that is more effective and more tolerable than interferon-based therapy to effectively treat interferon-ineligible-naïve/intolerant patients and nonresponder patients

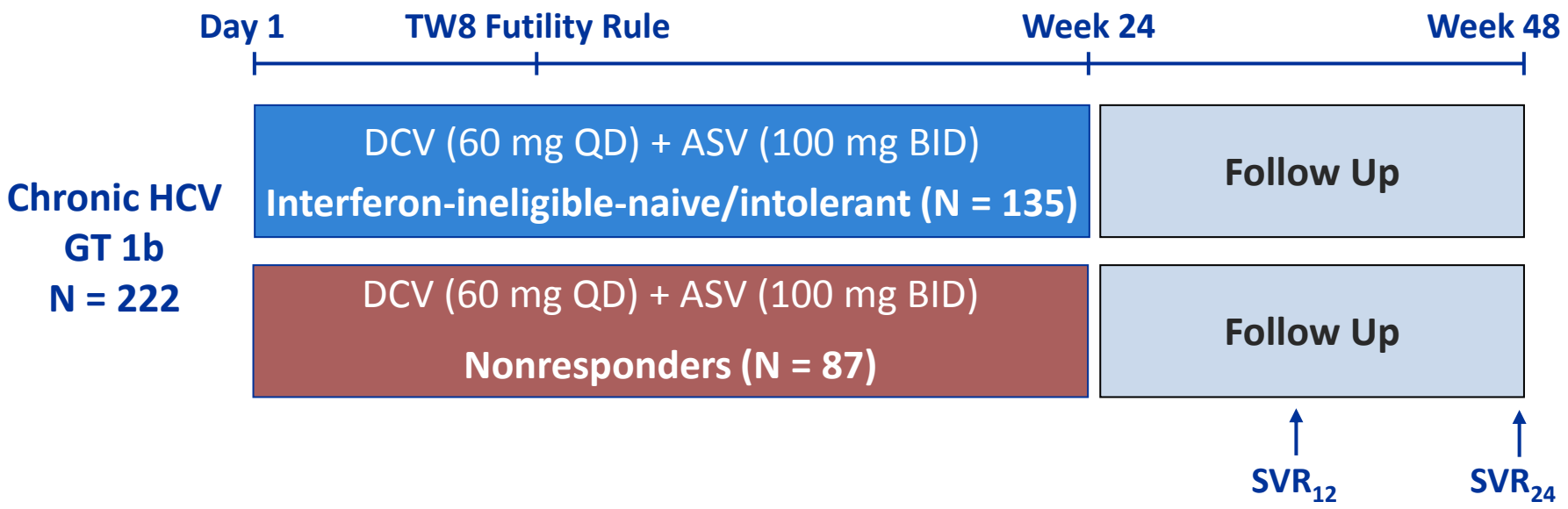
[1]Nagao Y et al. Office of Pharmaceutical Industry Research, Pager research series. 2006; 32 (Japanese only)
[2]Hayashi N et al. *J Viral Hepat* 2012;19:e134-42

Background: Daclatasvir and Asunaprevir

- Daclatasvir (DCV; BMS-790052) is a potent NS5A replication complex inhibitor with pan-genotypic (genotypes 1–6) antiviral activity *in vitro*[1,2]
- Asunaprevir (ASV; BMS-650032) is a potent NS3 protease inhibitor with antiviral activity against HCV genotypes 1, 4, 5, and 6 *in vitro*[3,4]
- Phase 2 studies showed potent antiviral effects using DCV and ASV as dual oral therapy and in combination with peginterferon/RBV in patients with HCV genotype 1 who were ineligible/intolerant to interferon-based therapies or had not responded to prior therapy[5,6]
- Presented here are results from the phase 3 confirmatory study of dual oral therapy, which have been submitted for registrational review

1. Gao M et al. *Nature* 2010;465:96-100; 2. Scheel TKH et al. *Gastroenterology* 2011;140:1032–42; 3. McPhee F et al. *Antimicrob Agents Chemother* 2012;56:5387-96. 4. Pasquinelli C et al. *Antimicrob Agents Chemother* 2012;56:1838-44; 5. Lok AS, et al. *N Engl J Med* 2012;366:216-24; 6. Chayama K et al. *Hepatology* 2012;55:742-8.

Open-Label, Parallel-Group Phase 3 Study (AI447-026)



- 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
- Study population included Japanese patients infected with HCV genotype 1b who were interferon-ineligible/intolerant or nonresponders (null and partial) to peginterferon/RBV, and included patients with cirrhosis (≈ 10%)
- No comparator group was included due to inability of patients to tolerate the current standard of care (IFN-ineligible/intolerant patients) and due to the relatively low anticipated efficacy of the current standard of care (prior nonresponder patients)

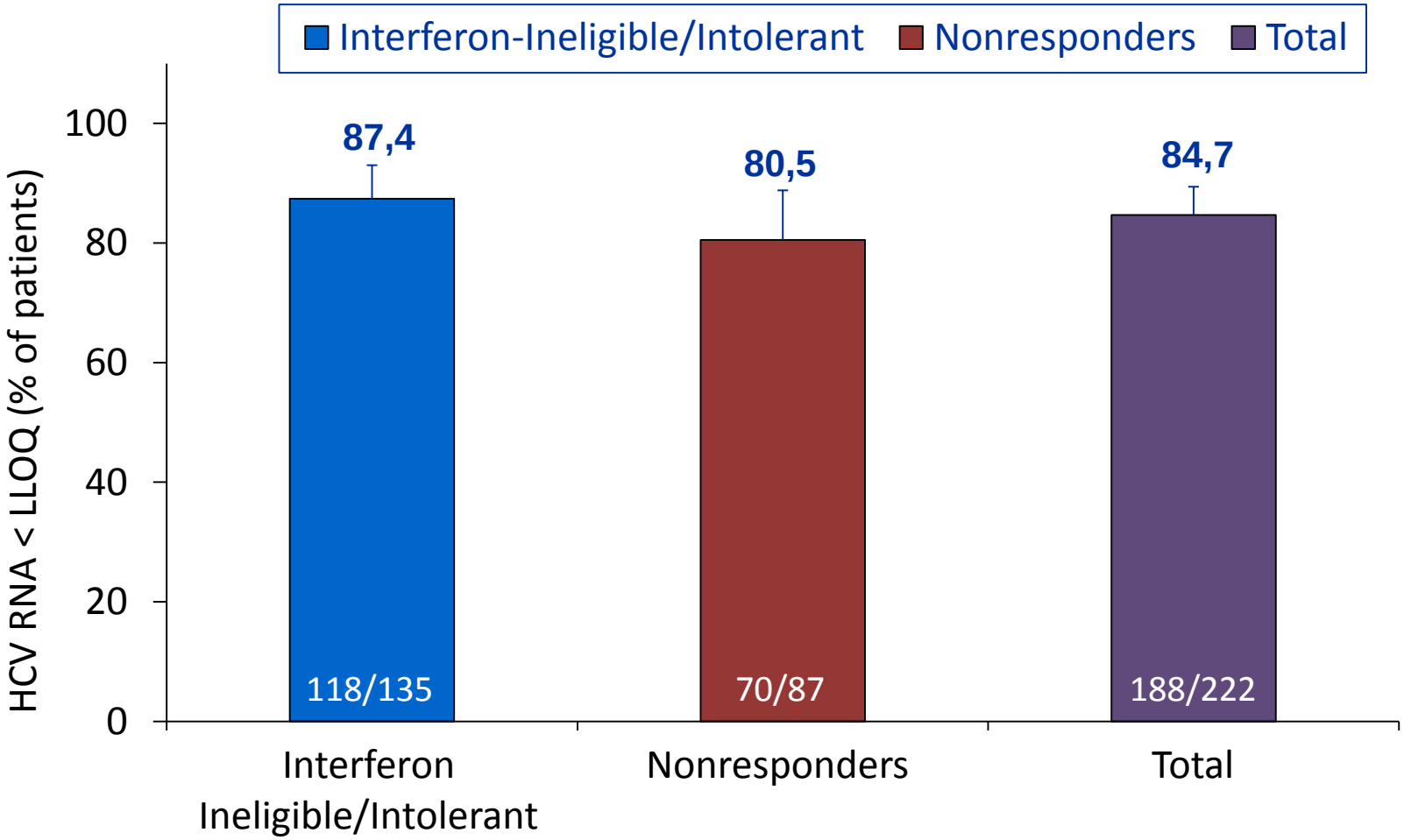
Patient Demographic Characteristics

Parameter		Interferon-Ineligible/Intolerant (N = 135)	Nonresponder (N = 87)	Total (N = 222)
Age, median years (range)		64.0 (24-75)	60.0 (42-74)	62.5 (24-75)
Age ≥ 65 years, n (%)		62 (46)	27 (31)	89 (40)
Male, n (%)		38 (28)	39 (45)	77 (35)
IL28B (rs12979860), n (%)	CC	94 (70)	16 (18)	110 (50)
	CT	40 (30)	66 (76)	106 (48)
	TT	1 (1)	5 (6)	6 (3)
HCV RNA, $\log_{10}$ IU/mL mean (SD)		6.6 (0.58)	6.8 (0.47)	6.6 (0.55)
Cirrhosis,[a] n (%)		11 (8)	11 (13)	22 (10)
Interferon-Ineligible/Intolerant, n (%)				
• Ineligible-naïve[b]		100 (74)	NA	100 (45)
• Intolerant to interferon/ribavirin[c]		35 (26)	NA	35 (16)
Nonresponders,[d] n (%)				
• Null responders		NA	48 (55)	48 (22)
• Partial responders		NA	36 (41)	36 (16)

[a]*Cirrhosis documented either by liver biopsy or discriminated by a previously described algorithm;* [b]*Included patients with depression, anemia, neutropenia, thrombocytopenia, hypertension, diabetes, autoimmune disease, and the elderly (>65 yrs) w/o comorbidities;* [c]*Defined as patients who received interferon-based therapy for <12 weeks and previously discontinued from therapy due to toxicities associated with interferon/ribavirin;* [d]*3 patients were undetermined by protocol*

- Many patients were older than 65 years (40%), with high viral loads, and a lower frequency of non-CC *IL28B* genotype among interferon-ineligible/intolerant and higher frequency of non-CC *IL28B* among nonresponder patients

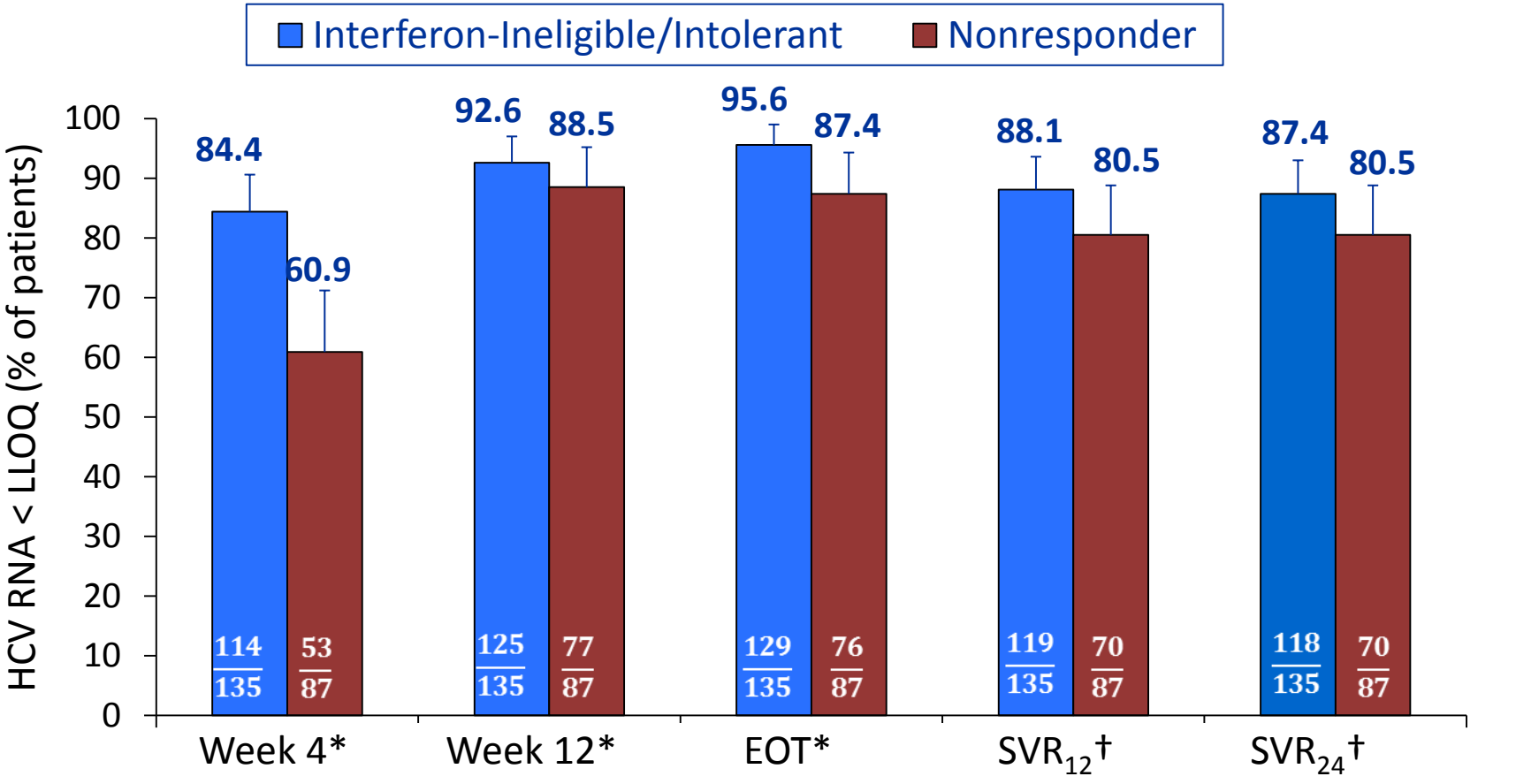
Primary Endpoint (mITT*): SVR_{24} (%)



**mITT: modified intent-to-treat, all treated subjects*

- High rates of SVR_{24} were achieved in both patient populations, those with limited therapeutic options and those typically associated with poor responses to other therapies

Virologic Response During and After Treatment

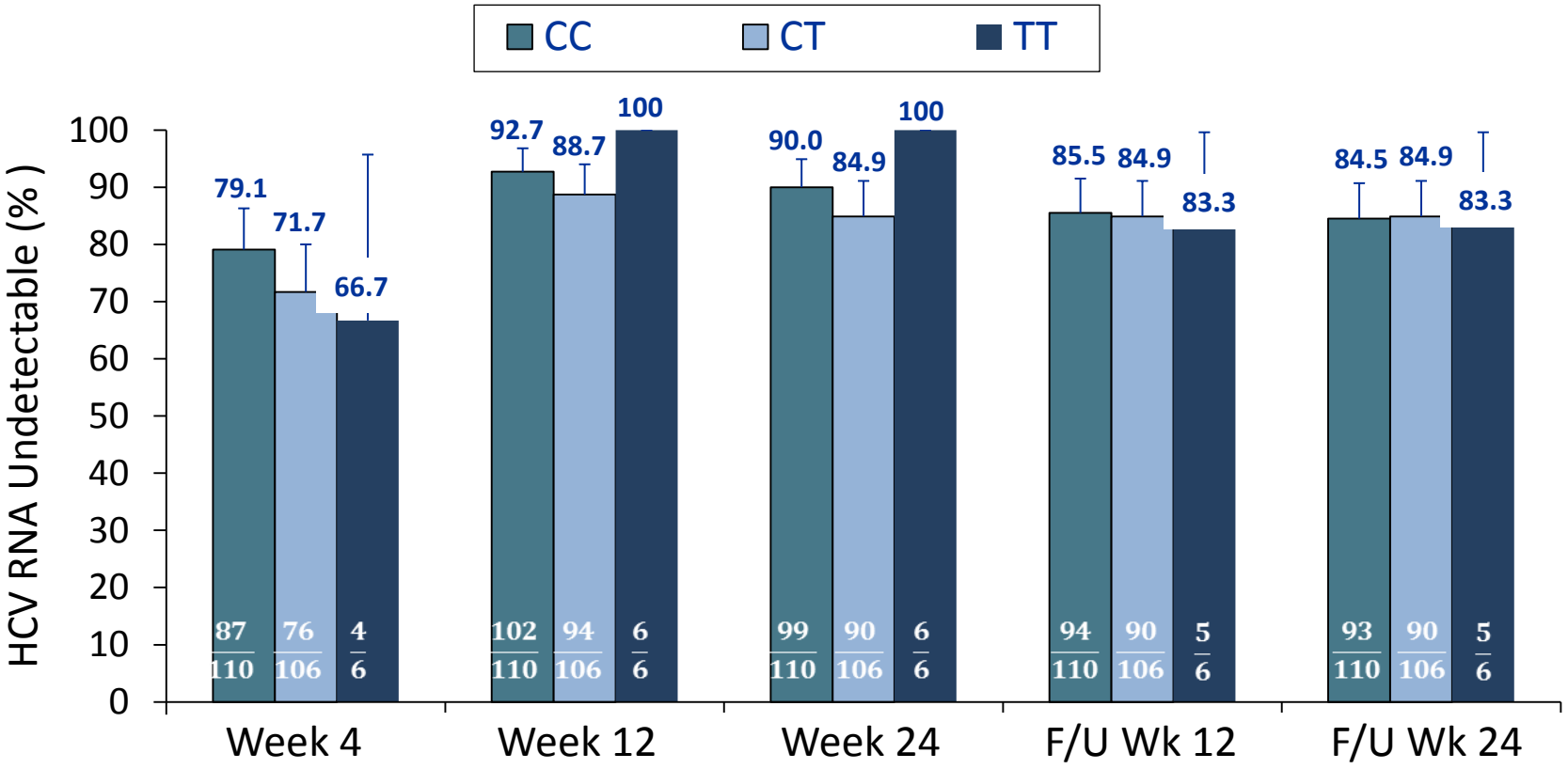


*On-treatment responses
HCV RNA < LLOQ (15 IU/mL), target not detected

† Posttreatment responses
HCV RNA < LLOQ, target detected or target not detected

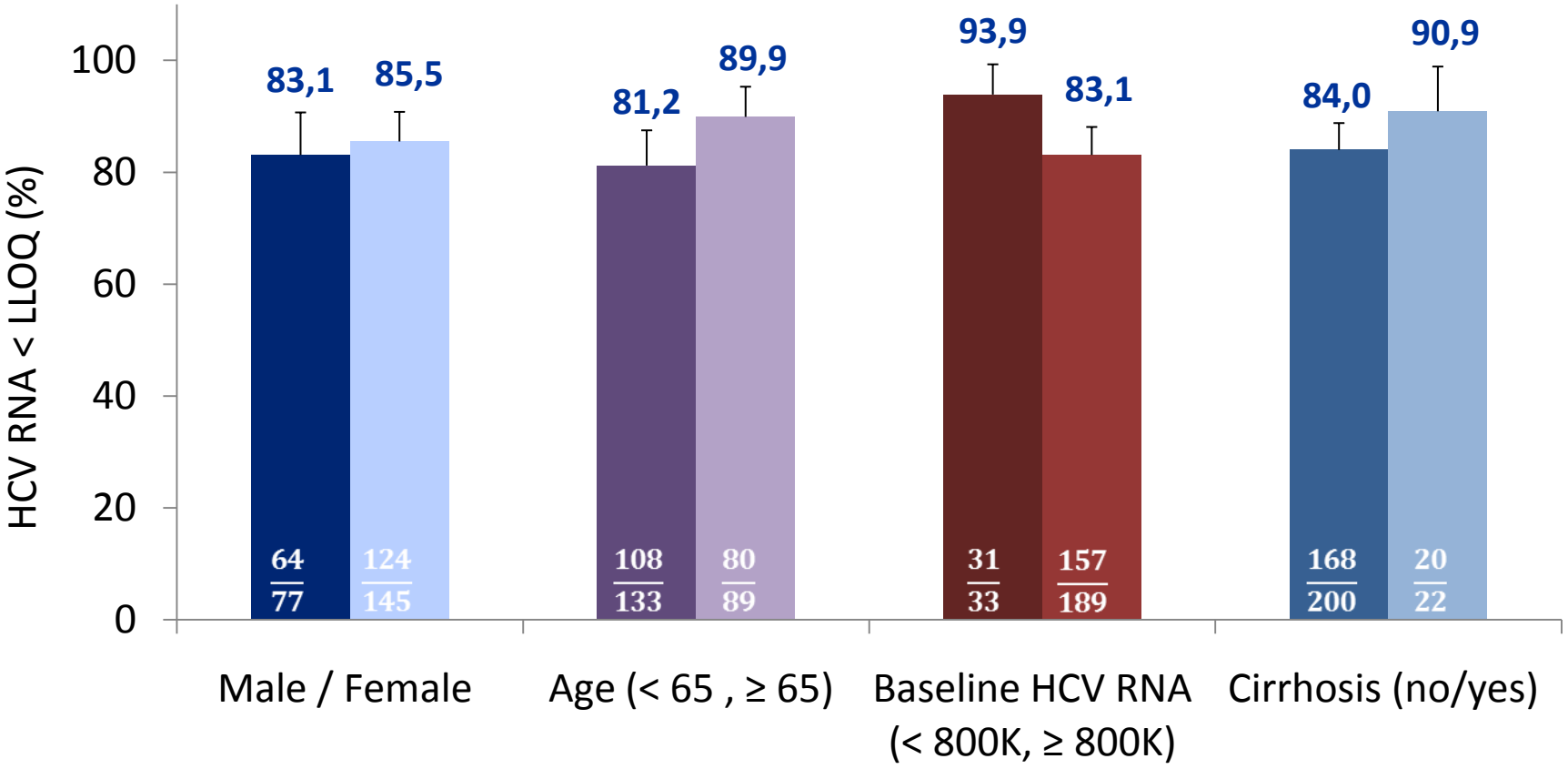
- Both treatment groups showed a rapid virologic response
- High rates of SVR were observed with high concordance between SVR_{12} and SVR_{24}

Summary of Undetectable HCV RNA by *IL28B* Genotype (rs12979860)



- High rates of sustained virologic response were achieved at all time points both on treatment and posttreatment regardless of *IL28B* genotype

Summary of SVR_{24} (%) by Baseline Factors



- Baseline factors, including male gender, advanced age, high baseline HCV RNA, and cirrhosis, did not appear to impact response rates
- 91.9% (57/62) of interferon-ineligible/intolerant patients ≥ 65 years of age achieved SVR_{24}

Patient Disposition

n (%)	Interferon-Ineligible/Intolerant	Nonresponder	Total
Treated patients	135	87	222
Completed treatment	121 (89.6)	73 (83.9)	194 (87.4)
Discontinued treatment	14 (10.4)	14 (16.1)	28 (12.6)
Lack of efficacy	4 (3.0)	11 (12.6)[a]	15 (6.8)
Adverse Events	9 (6.7)	2 (2.3)	11 (5.0)
Patient request	1 (0.7)	1 (1.1)	2 (0.9)

[a] 9 nonresponder patients received additional treatment with peginterferon/RBV

- No deaths, and study discontinuation rate was low
- SVR_{24} was achieved in 8/10 (80%) patients who discontinued because of LFT elevations; all had been on treatment ranging from 4 to 23 weeks
- Low rates of virologic breakthrough and EOT detectable HCV RNA (17 patients [7.7%]), and low rates of relapse (17/205 [8.3%] among patients with undetectable HCV RNA at EOT)
  - Failures were associated with emergence of NS5A and NS3 resistance-associated variants *(See AASLD Poster 1111 McPhee F et al.)*

On-Treatment Adverse Events (Any Grade) and Grade 3 or 4 Laboratory Abnormalities

n (%)	Interferon-Ineligible/Intolerant (N = 135)	Nonresponder (N = 87)	Total (N = 222)
Serious adverse event (on treatment)	9 (6.7)	4 (4.6)	13 (5.9)
Common adverse events (> 10% of patients)			
Nasopharyngitis	40 (29.6)	27 (31.0)	67 (30.2)
Increased alanine aminotransferase	24 (17.8)	11 (12.6)	35 (15.8)
Increased aspartate aminotransferase	18 (13.3)	10 (11.5)	28 (12.6)
Headache	18 (13.3)	17 (19.5)	35 (15.8)
Diarrhea	12 (8.9)	10 (11.5)	22 (9.9)
Pyrexia	12 (8.9)	15 (17.2)	27 (12.2)
Grade 3-4 laboratory abnormalities (> 3%)			
Increased alanine aminotransferase	12 (8.9)	4 (4.6)	16 (7.2)
Increased aspartate aminotransferase	10 (7.4)	2 (2.3)	12 (5.4)
Hemoglobin	6 (4.4)	1 (1.1)	7 (3.2)

- Daclatasvir and asunaprevir were well tolerated for 24 weeks of therapy
- Low rates of SAEs, common AEs, and Grade 3-4 laboratory abnormalities were observed

Conclusions

- All-oral combination of daclatasvir and asunaprevir achieved high rates of SVR_{24} in Japanese patients without treatment options and in patients with no prior response to interferon-based therapy
  - 87.4% in interferon-ineligible/intolerant patients
  - 80.5% in prior nonresponder patients
- Traditional baseline factors including gender, age, baseline HCV RNA, cirrhosis, and *IL28B* genotype did not impact response rates
- This all-oral, interferon-free, ribavirin-free regimen was well tolerated with low rates of discontinuation, representing a clinically meaningful improvement in both safety and efficacy compared to current standard of care

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