DACLATASVIR PLUS SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN IN PATIENTS WITH HIV-HCV COINFECTION: INTERIM ANALYSIS OF A FRENCH MULTICENTER COMPASSIONATE USE PROGRAM (AI444-258)

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Disclosures

- Pr. Salmon has been a speaker and invited to conferences on behalf of Gilead, Bristol-Myers Squibb, and ViiV, and has participated in scientific boards for Gilead and Bristol-Myers Squibb

- Bristol-Myers Squibb provided daclatasvir for patients included in the French Temporary Authorization For Use program (ATU)

Background

- **Daclatasvir (DCV)**
  - Pangenotypic[a] NS5A inhibitor; low potential for drug-drug interactions
  - Safe and well tolerated
  - Studied in > 13,000 patients
  - Approved in Europe, Japan, multiple nations across Latin America, the Middle East and Asia Pacific; under regulatory review in the US
- **Sofosbuvir (SOF)**
  - Pangenotypic NS5B inhibitor; low potential for drug-drug interactions
  - Safe and well tolerated
  - Approved in combination with other HCV agents the US, Europe, and Canada

- The all-oral 12 weeks regimen of DCV + SOF was well tolerated and achieved 97% SVR12 in HIV/HCV coinfected patients receiving a wide range of antiretroviral agents in the phase 3 ALLY-2 study[1]

[a] Pangenotypic: GT 1-6 *in vitro* and GT 1-4 in clinical trials.

[1]Wyles DL, et al. *NEJM* 2015; DOI: 10.1056/NEJMoa1503153.

Objective

- **French compassionate use program (CUP):**
  - DCV was provided before commercialization to HCV-infected patients without available treatment options
  - Patients with advanced liver disease ± HIV coinfection were included at multiple centers (March 28 – October 24, 2014)

- **Recommended regimen and treatment duration**:
  - DCV 60 mg + SOF 400 mg for 24 weeks
  - DCV dose adjustment with cART: boosted PIs (30 mg); NNRTI except RPV (90 mg)
  - Ribavirin (RBV) use and shorter treatment duration (12 weeks) at physician's discretion

- **Interim analysis objective:**
  - To evaluate the efficacy and safety of DCV + SOF ± RBV in HIV/HCV coinfected patients (by treatment duration and regimen; HCV genotype; and cirrhosis status)

Patient Population

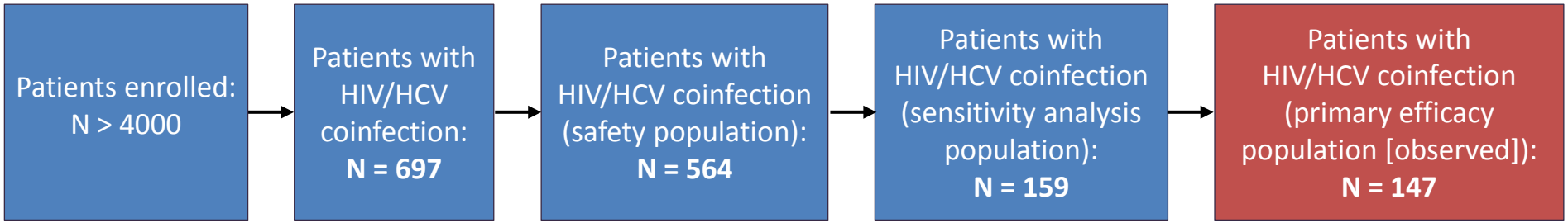
- Daclatasvir was authorized for patients with chronic HCV infection (all genotypes):
  - Age > 18 years
  - Advanced liver disease with no alternative HCV treatments available:
    - Metavir score ≥ F3, or < F3 with HCV extrahepatic manifestations, or
    - Post-liver transplant HCV recurrence, or
    - Indication for liver / kidney transplantation

- Daclatasvir was contraindicated in cases of:
  - Pregnancy
  - Allergy to DCV or excipients
  - Coadministration with concomitant medication that strongly induce CYP3A4 or P-glycoprotein

Endpoints and Analysis Populations

- **Endpoints**
  - Efficacy: sustained virologic response (SVR12)* at post-treatment Week 12 (PT12)
  - Safety: based on SAEs and AEs leading to discontinuation

- **Analysis populations**
  - Primary efficacy population (observed): all patients with available HCV RNA assessments at PT12
  - Sensitivity analysis population: all patients with available HCV RNA assessments at PT12, and patients with HCV RNA detectable at PT4 but without PT12 data available (considered as virologic failures at PT12)
  - Safety population: patients with ≥ 1 completed visit form



*SVR12 was defined as HCV RNA < lower limit of quantification [LLOQ], target detected [TD] or target not detected [TND].

Baseline Characteristics / Demographics

Parameter	Patients with HCV RNA assessments at PT12 (Efficacy population [observed] N = 147)*
Median age, years (range)	52 (34–71)
Male, n (%)	106 (73.1)
Cirrhosis, n (%)†	110 (76.4)
HCV RNA, log median IU/mL (range)	6.07 (1.38–7.83)
HCV genotype, n (%)‡	
1¶	101 (70.6)
1a / 1b	73 (50.7) /23 (16.0)
3	14 (9.8)
4	28 (19.6)
HCV treatment experienced, n (%)	123 (85.4)
DCV dose, n (%)	
30 mg	49 (33.3)
60 mg	88 (59.9)
90 mg	10 (6.8)
Treatment duration 12 / 24 weeks , n (%)	46 (31.3) /100 (68.0)
Duration not reported, n (%)	1 (0.7)
RBV use, n (%)	14 (9.5)

- The majority of patients were male and cirrhotic (87% Child-Pugh class A, 12% class B, 0.9% class C)

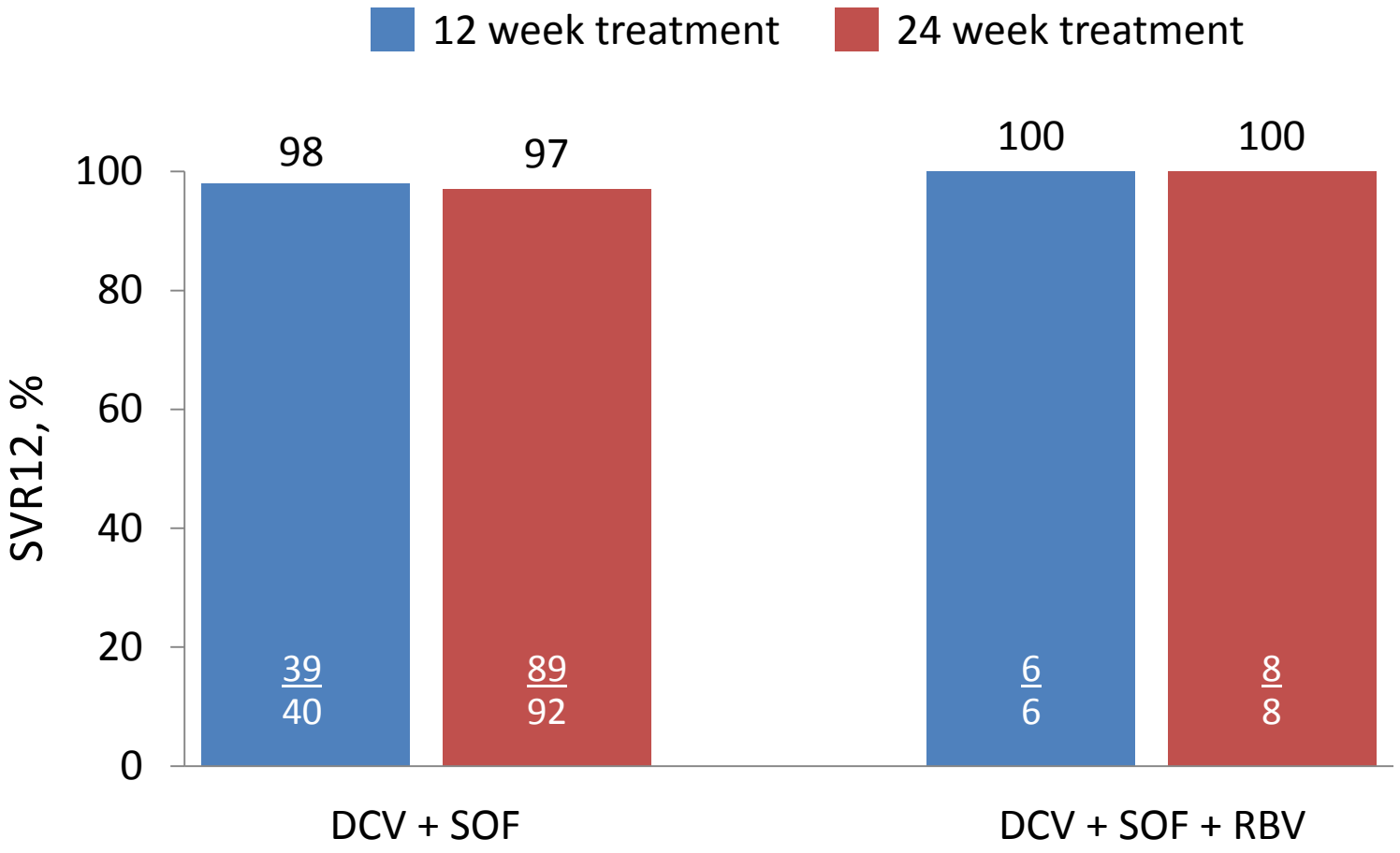
* Data missing for gender (2 patients), cirrhosis (3), HCV RNA (1), HCV GT (3), treatment experience (3). Percentages based on available data.
† Cirrhosis was determined by the physician using liver biopsy (METAVIR > F3), Fibroscan (> 14.6 kPa) or Fibrotest (> 0.74).
‡ One patient had mixed HCV GT 1b/3. ¶ Includes 5 patients with unspecified GT 1 subtype.

HIV Characteristics and Regimens

Parameter	Patients at PT12 (N = 147)
HIV RNA < 200 copies/mL, n (%)	121 (100)*
CD4 cells per mm^3, mean (SD)	592 (349)*
Antiretroviral regimen, n (%) †‡	143
Non-nucleoside reverse transcriptase inhibitor	34 (23.8)
Etravirine	12 (8.4)
Rilpivirine	20 (14.0)
Efavirenz	2 (1.4)
Protease inhibitor	51 (35.7)
Darunavir/r	18 (12.6)
Atazanavir/r	25 (17.5)
Others	9 (6.3)
Integrase inhibitor	92 (64.3)
Raltegravir	87 (60.8)
Dolutegravir	5 (3.5)
Not reported	4 (2.7)

* Data missing for 26 patients (HIV RNA) and 14 patients (CD4 count). Percentages based on available data.
† Multiple HIV regimens may have been recorded for individual patients.
‡ DCV dose adjusted to 30 mg QD with PI regimens and 90 mg QD with NNRTIs; some patients received PI + NNRTI with DCV 60 mg.
SD, standard deviation

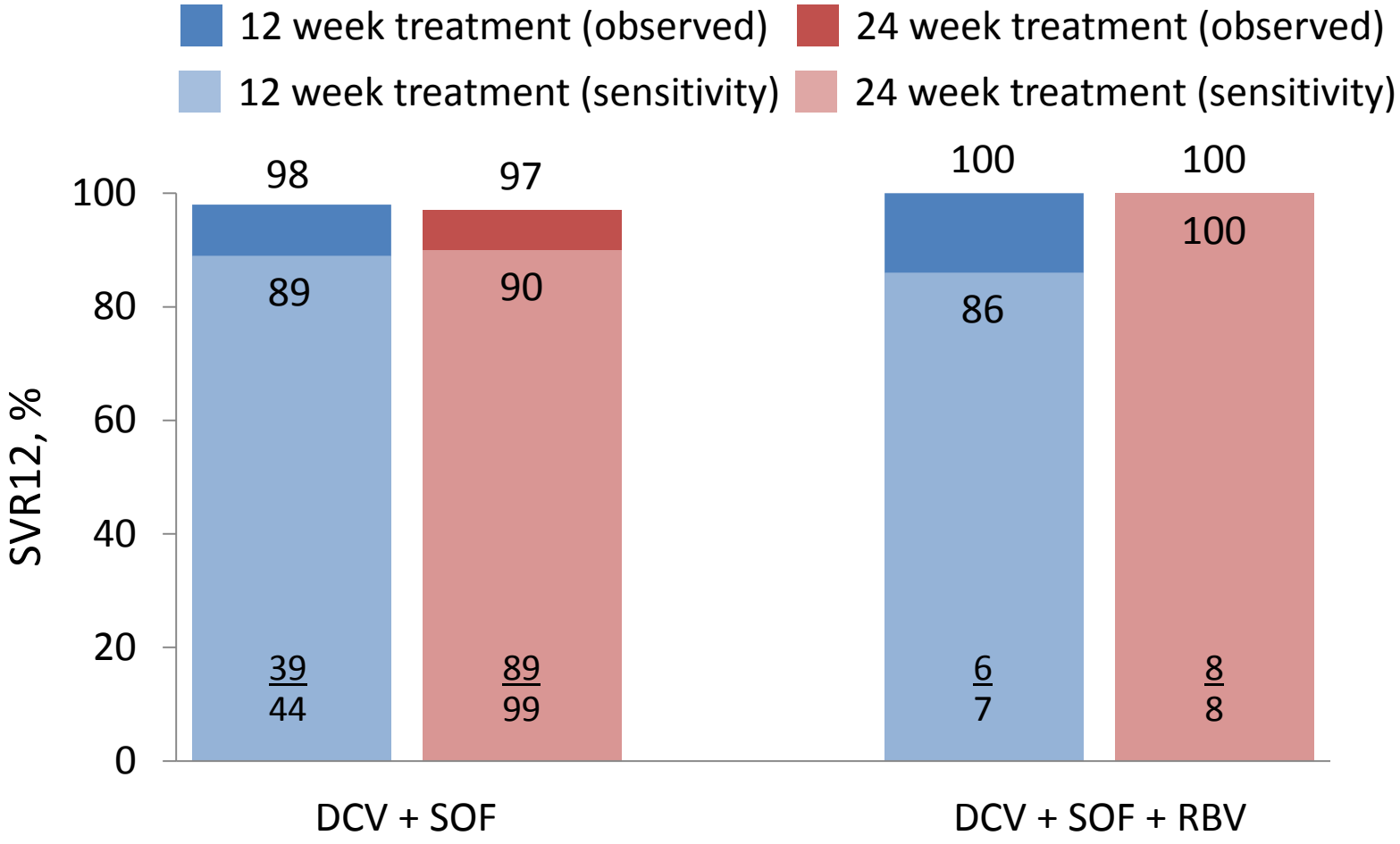
SVR12 by Treatment Regimen and Duration of Treatment: Observed Population



- Overall SVR12 rate was 97% (as observed, 143/147)*
- SVR12 rates suggest no benefit with the addition of RBV or extending treatment duration to 24 weeks

* Treatment duration was not reported in one patient.

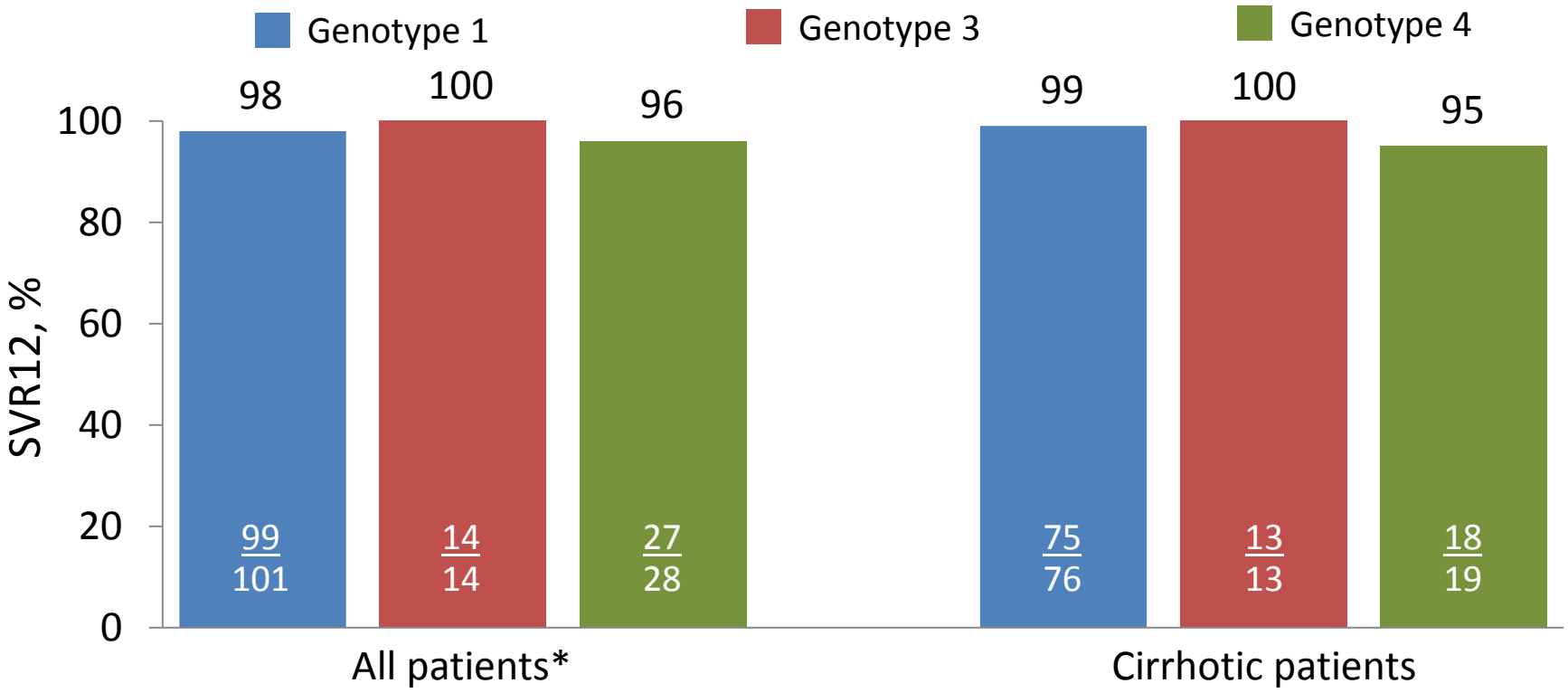
SVR12 by Treatment Regimen and Duration of Treatment: Sensitivity Analysis Population



- Sensitivity analysis showed similar overall trends with the observed analysis
- Overall SVR12 rate was 90% (sensitivity analysis, 143/159)

Treatment duration was not reported in one patient.
Sensitivity analysis: all patients with available HCV RNA assessments at PT12, and patients with HCV RNA detectable at PT4 but without PT12 data available (considered as virologic failures at PT12). n/N values indicate results for the sensitivity analysis.

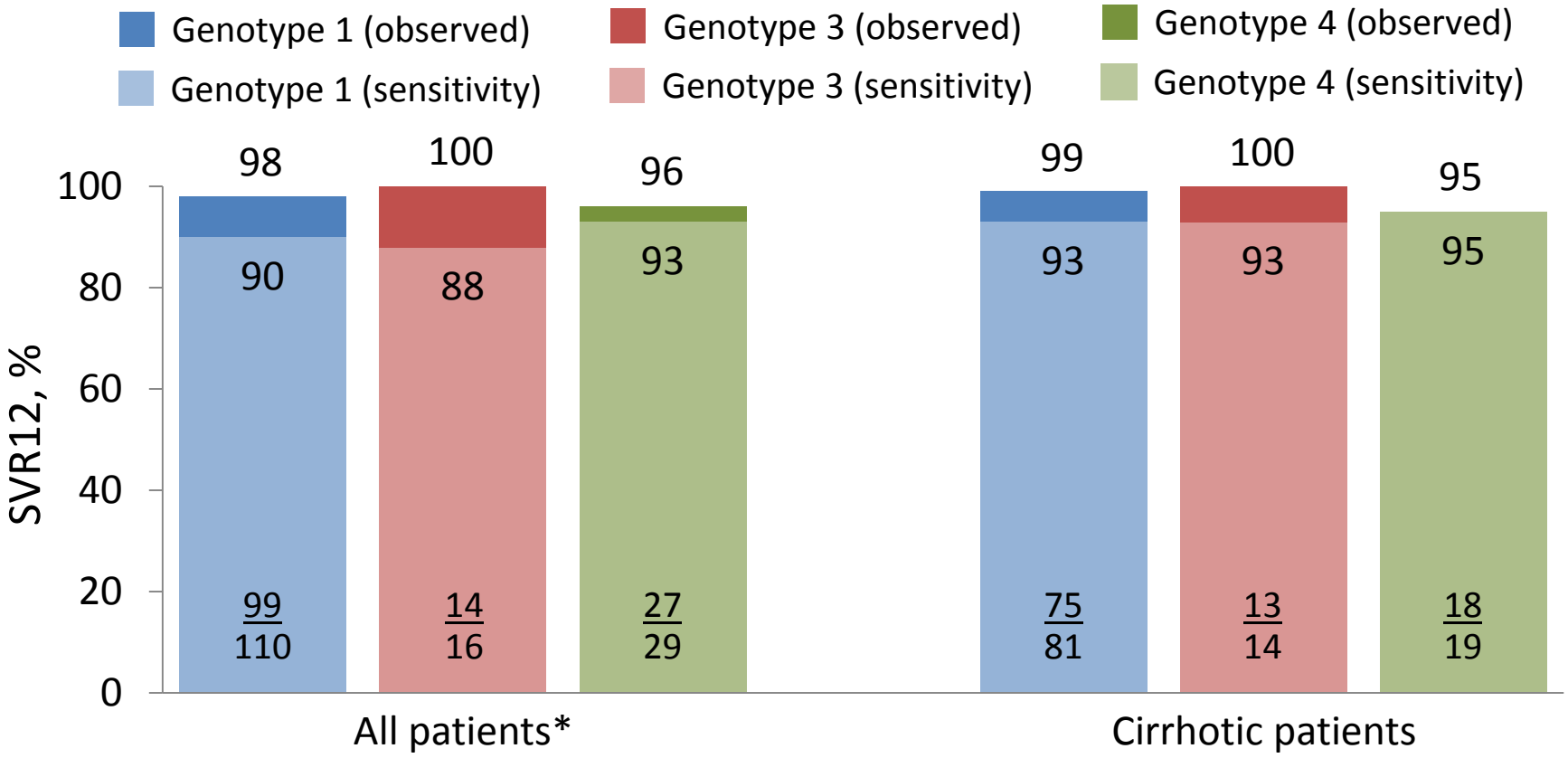
SVR12 by HCV Genotype and Cirrhosis Status: Observed Population



- High SVR12 rates were observed regardless of HCV genotype or cirrhosis status
- Among GT-1 cirrhotic patients, no apparent benefit of RBV use or extending treatment duration to 24 weeks on SVR12:
  - DCV + SOF: 12 weeks, 100% (n= 15/15); 24 weeks, 98% (n = 52/53)
  - DCV + SOF + RBV: 12 weeks, 100% (n = 3/3); 24 weeks, 100% (n = 4/4)

Presented data include 12 or 24 weeks of treatment duration ± RBV.
Treatment duration was not reported in one patient.
*Three patients had undetermined HCV GT and one patient had mixed HCV GT1b/3 infection.

SVR12 by HCV Genotype and Cirrhosis Status: Sensitivity Analysis Population

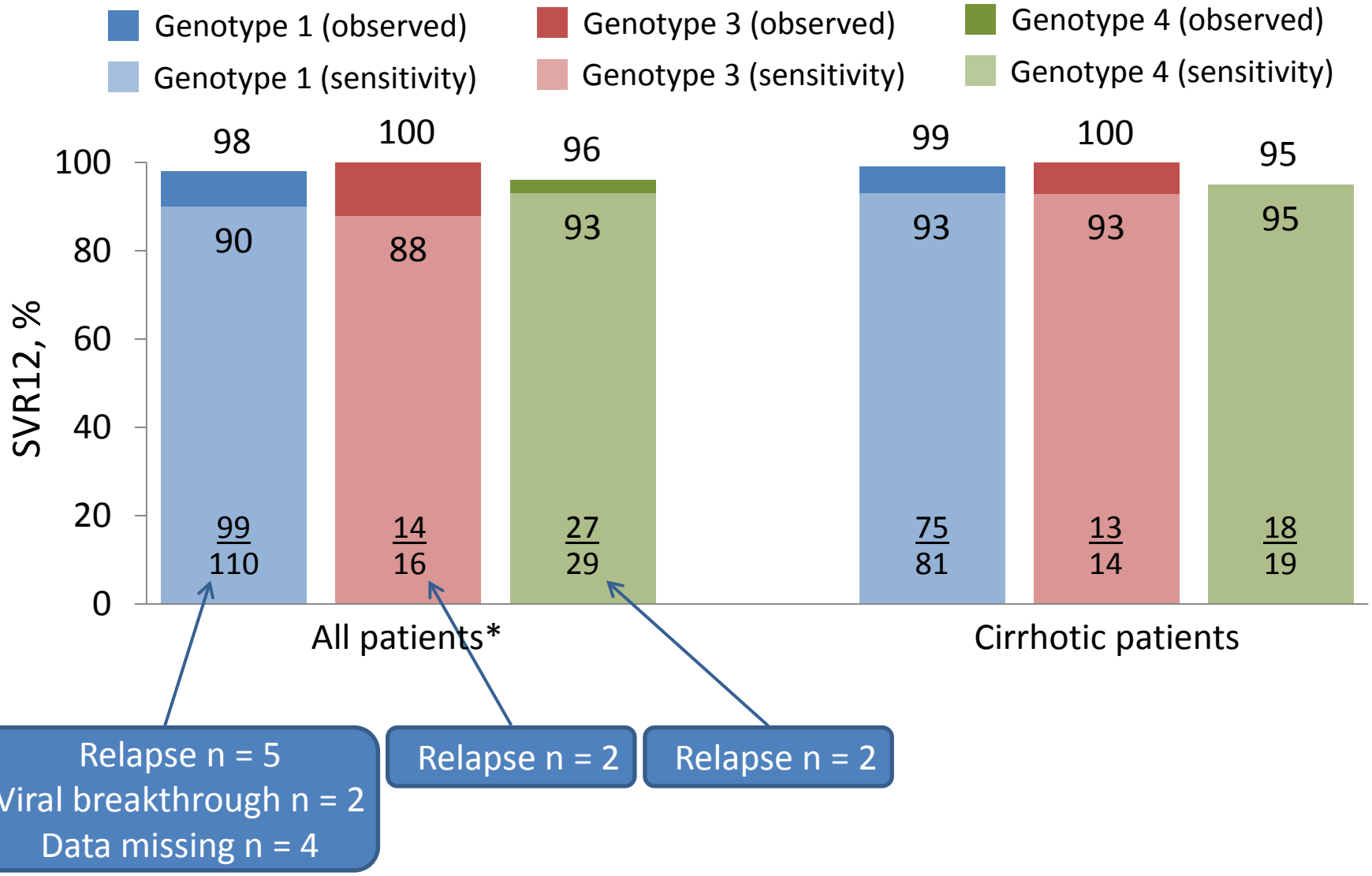


- Sensitivity analysis showed similar overall trends with the observed analysis

Sensitivity analysis: all patients with available HCV RNA assessments at PT12, and patients with HCV RNA detectable at PT4 but without PT12 data available (considered as virologic failures at PT12). n/N values indicate results for the sensitivity analysis.

*Three patients had undetermined HCV GT and one patient had mixed HCV GT1b/3 infection.

SVR12 by HCV Genotype and Cirrhosis Status: Sensitivity Analysis Population



Virologic failure data are based on the sensitivity population.
Viral sequencing data are not available for analysis of virologic failures.
*Three patients had undetermined HCV GT and one patient had mixed HCV GT1b/3 infection.

Safety and Tolerability

Event, n (%)	Total (N=564)
Deaths [a]	9 (1.6)
Serious adverse events	22 (3.9)
Likely related to HCV therapy [b]	2 (0.4)
Likely unrelated to HCV therapy	20 (3.5)
Cardiac	2 (0.4)
Pulmonary	2 (0.4)
Renal	2 (0.4)
Gastrointestinal	1 (0.2)
Liver disease/hepatocellular carcinoma	6 (1.1)
HIV related	2 (0.4)
Others	5 (0.9)
Discontinuations due to adverse events [c]	2 (0.4)

a. 7 deaths were considered not treatment related (single cases of hepatocellular carcinoma, respiratory distress, fall/intracerebral hematoma, septic shock, road traffic accident, and 2 deaths with unknown cause); 2 deaths causality not reported (multi-organ failure and hepato-renal failure)

b. Serious AEs likely related: 1 case of life-threatening bundle branch block associated with bradycardia and syncope in a 58 year-old male, cirrhotic, tobacco-user treated with efavirenz/emtricitabine/tenofovir; the event occurred 6 days after initiation of DCV+SOF, HCV therapy was maintained and the patient recovered from syncope; bundle branch block and bradycardia resulted in pacemaker placement. 1 case of creatine phosphokinase increase in a 51 year-old male, cirrhotic patient treated with emtricitabine/tenofovir + raltegravir; HCV therapy was maintained.

c. Asthenia led to discontinuation in two cases; 1 stopped HCV therapy on Day 43 and 1 stopped at 12 weeks with undetectable HCV RNA (investigator's decision).

- No compromise of HIV control
  - Mean CD4 cells/mm^3 and proportion with HIV RNA < 200 c/mL were similar at baseline and PT12

Summary

- DCV + SOF provided high SVR12 rates in this real-world, interim analysis in HIV/HCV coinfected patients
  - No benefit of extending treatment duration from 12 to 24 weeks
  - No apparent benefit from the addition of RBV
  - Sensitivity analysis showed similar overall trends with the observed analysis
- Comparable SVR12 rates (≥ 95%) regardless of HCV genotype (1, 3, or 4) or cirrhosis status
- DCV + SOF ± RBV was generally well tolerated and compatible with a wide range of antiretrovirals
- No compromise of HIV control
- These results in HIV/HCV coinfected patients with severe liver disease are consistent with the findings from the ALLY-2 study[1]

[1]Wyles DL, et al. *NEJM* 2015; DOI: 10.1056/NEJMoa1503153

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