Shortening overall treatment to 12 weeks of simeprevir plus PR in treatment-naïve chronic hepatitis C genotype 1 patients: assessment of baseline and Week 2 on-treatment predictors of SVR

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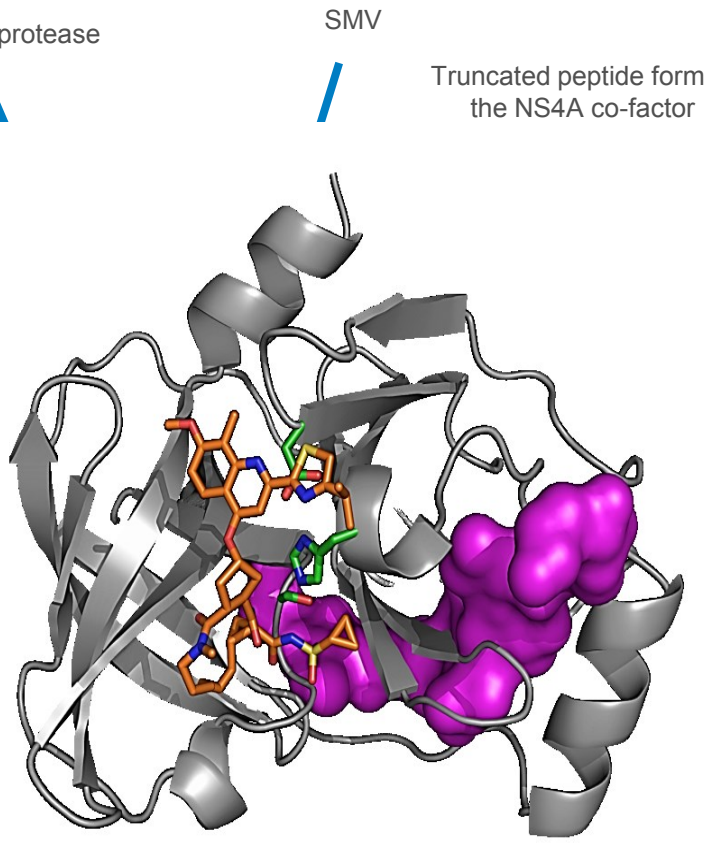
Disclosures

- Tarik Asselah is a speaker and investigator for AbbVie, BMS, Janssen, Gilead, Roche and MSD

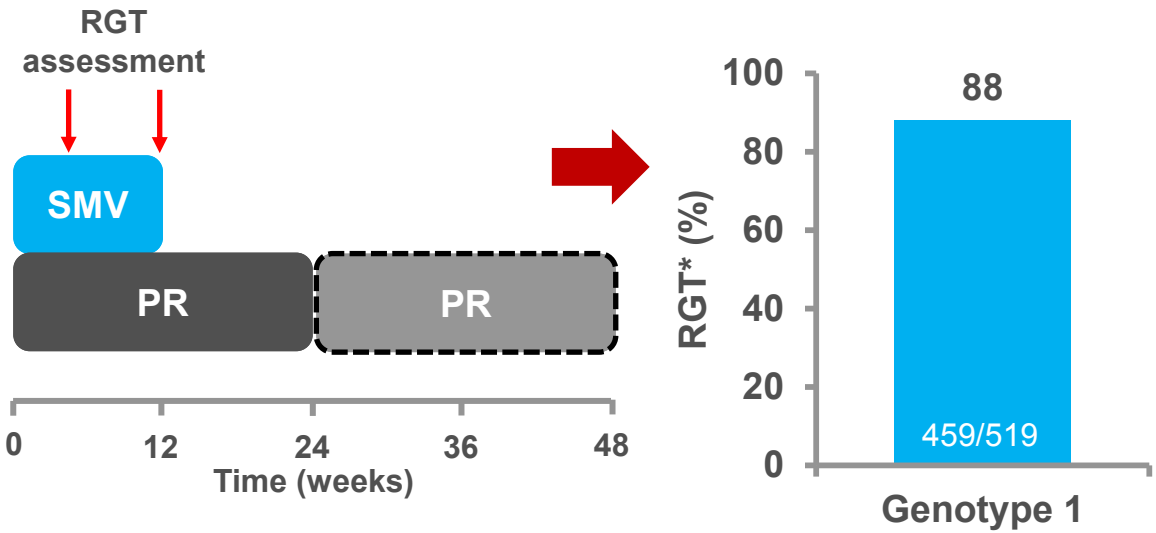
Simeprevir (SMV)



- Once-daily capsule, HCV NS3/4A protease with pan-genotypic activity with the exception of genotype 3[1,2]
- Approved in the EU, Japan, Canada, Russia, USA and in other regions
  - Approved in the EU and USA in combination with PegIFN or SOF for HCV genotype 1 and genotype 4[3]
- Ongoing clinical development in IFN-free combinations in genotypes 1 and 4[4]
- Good safety and tolerability profile in clinical trials[5–8] and in real-world evidence studies[9–10]

1. Reesink et al. Gastroenterology 2010;138:913−21; 2. Moreno et al. J Hepatol 2012;56:1247−53
3. Simeprevir SmPCs; 4. clinicaltrials.gov; 5. Jacobson I. Lancet 2014;384:403–13
6. Manns et al, Lancet 2014;384:414–26; 7. Forns et al. Gastroenterology 2014;146:1669–79
8. Moreno et al. EASL 2014. Poster 1319; 9. Jensen et al. AASLD 2014. Oral 45 10. Dieterich et al. AASLD 2014. Oral 46

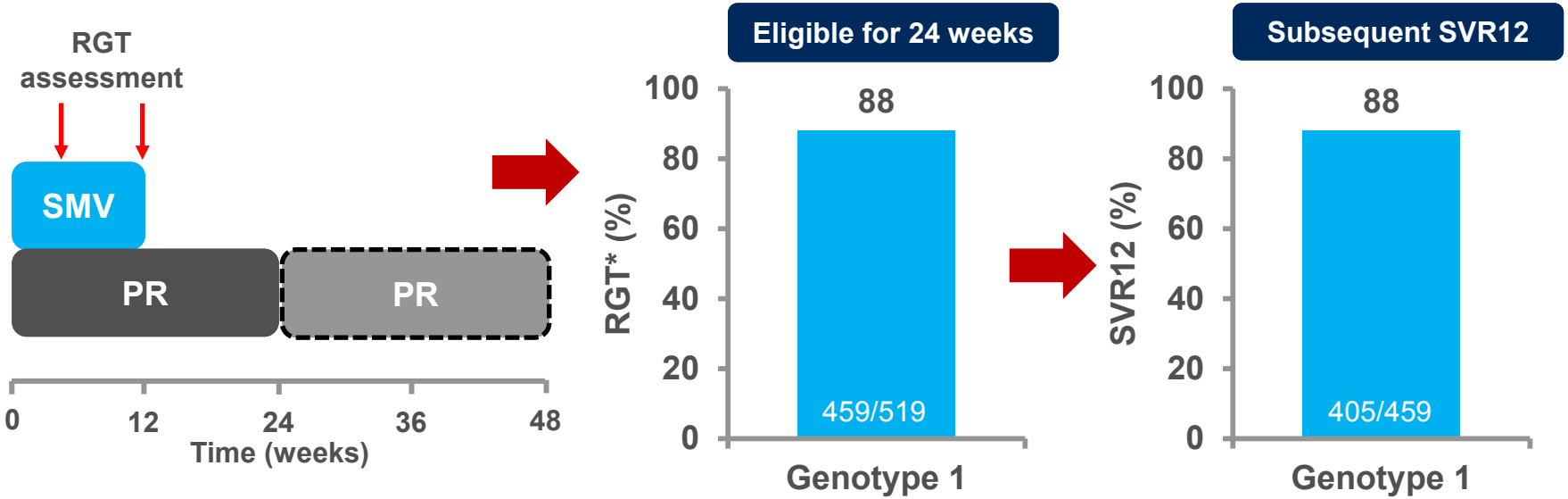
Background: treatment duration for SMV + PR in HCV genotype 1 treatment-naïve patients



*Determined by RGT: HCV RNA <25 IU/mL detectable or undetectable at Week 4 and undetectable at Week 12; RGT: response-guided therapy
RVR (HCV RNA undetectable at Week 4)

1. Jacobson I et al. AASLD 2013. Abstract 1122

Background: treatment duration for SMV + PR in HCV genotype 1 treatment-naïve patients



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Background: 12 weeks triple therapy with protease inhibitor in HCV genotype 1 patients

- CONCISE study (TVR + PR)[1]:
  - Treatment-naïve and prior relapsers with HCV genotype 1 and *IL28B* CC
  - 12 weeks of therapy, if RVR (week 4) achieved
  - SVR rate of 87%

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1. Nelson et al. EASL 2013. Poster presentation

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  - 12 weeks of therapy, if RVR (week 4) achieved
  - SVR rate of 87%

- In the current study, we investigated the possibility of shortening SMV + PR treatment to 12 weeks using an algorithm based on on-treatment response at **Week 2**, irrespective of baseline characteristics

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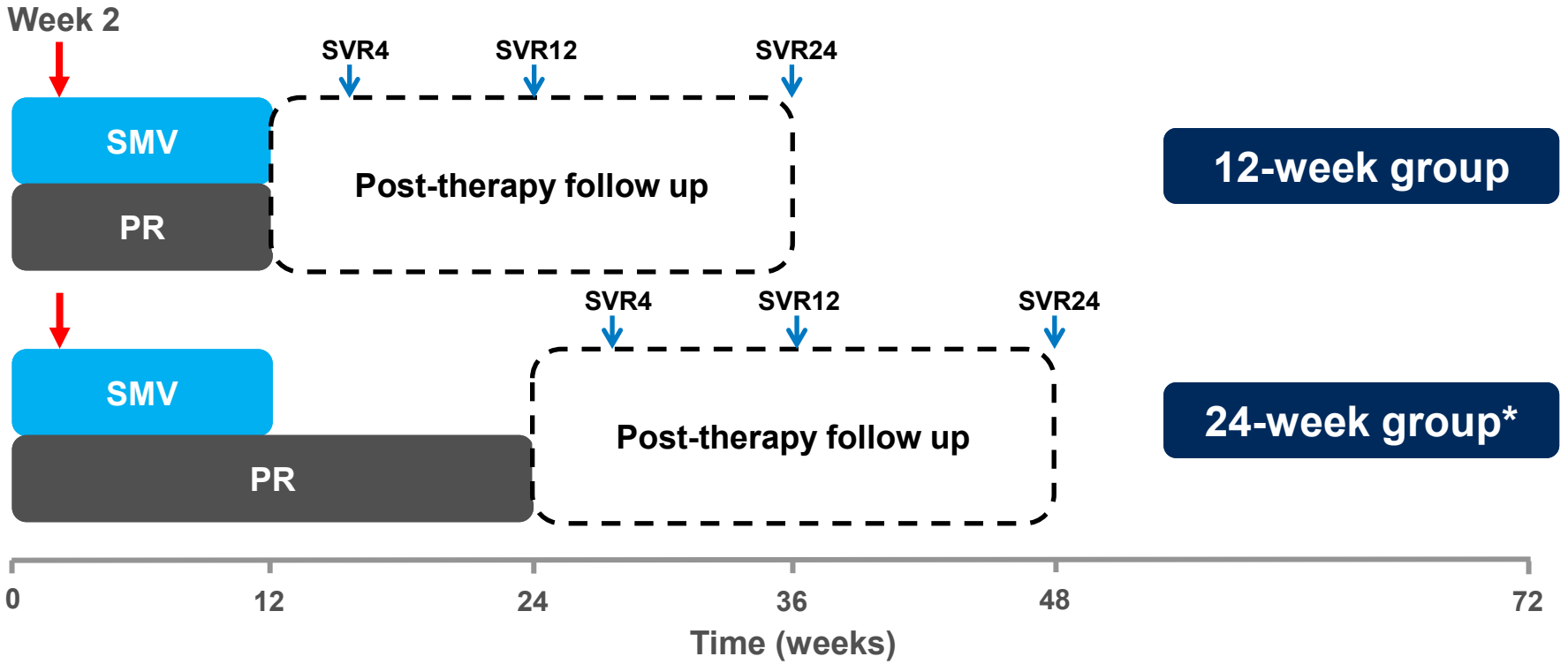
Study design (HPC3014; NCT 01846832)



- Patients meeting modified RGT criteria to stop all therapy after 12 weeks‡
- Patients not meeting modified RGT criteria will continue PR until Week 24
- Patients stopped all therapy if HCV RNA ≥25 IU/mL at Week 4

*Patients in France had the option to extend treatment to 48 weeks – this option was taken by one patient
Roche COBAS® Taqman® LLOQ:25 IU/mL, LOD: 15 IU/mL. Protocol amendment for genotype 4 patients: in those with *IL28B* CT or TT, HCV RNA <25 IU/mL (undetectable) at Week 2 was required to qualify for the 12-week treatment arm

Study objectives and population

Primary objective

- Evaluate the efficacy, tolerability, and safety of 12 weeks of treatment with SMV + PR in patients meeting modified RGT criteria

Population

- Treatment naïve adults with HCV genotype 1 or 4 monoinfection with mild to moderate fibrosis
  - METAVIR stage F0–F2 (biopsy or non-invasive methods)
  - All *IL28B* genotypes
- This presentation will show data from the GT1 cohort

Shortening overall treatment to 12 weeks of SMV + PR according to early virologic response in treatment-naive patients with chronic HCV genotype 4 infection and mild-to-moderate fibrosis
Presented 12 March: 17:48–17:55

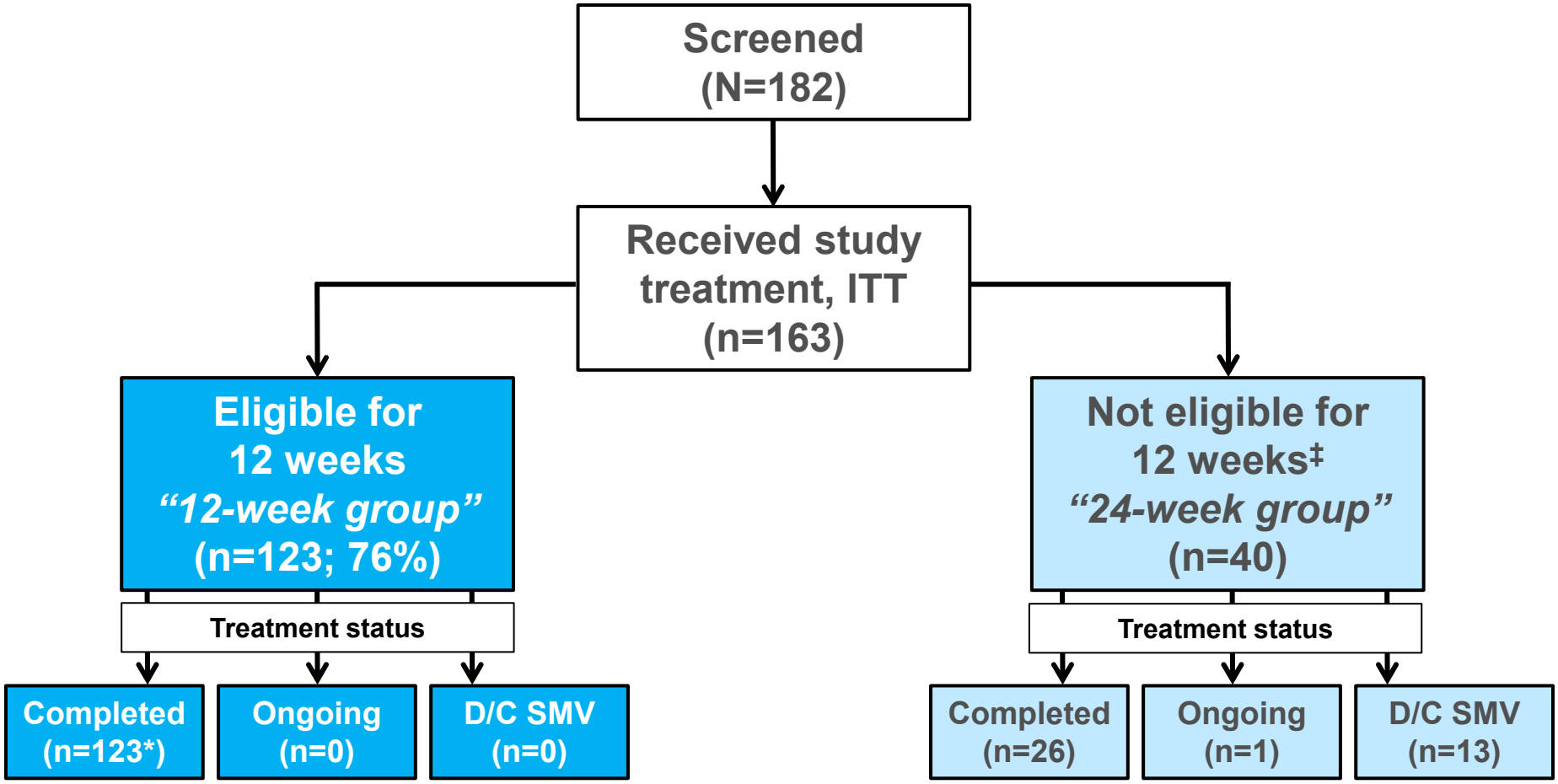
Treatment algorithm for genotype 1

IL28B genotype	HCV RNA at Week 2 of treatment	Treatment duration
All	< 25 IU/mL undetectable	12 weeks*
	< 25 IU/mL detectable	
	≥ 25 IU/mL detectable	24 weeks

*To qualify for 12 weeks patients must also be <25 IU/mL undetectable at Week 4 and Week 8

Patients stopped all therapy if HCV RNA ≥25 IU/mL at Week 4
Roche COBAS® Taqman® LLOQ:25 IU/mL, LOD: 15 IU/mL

Patient disposition



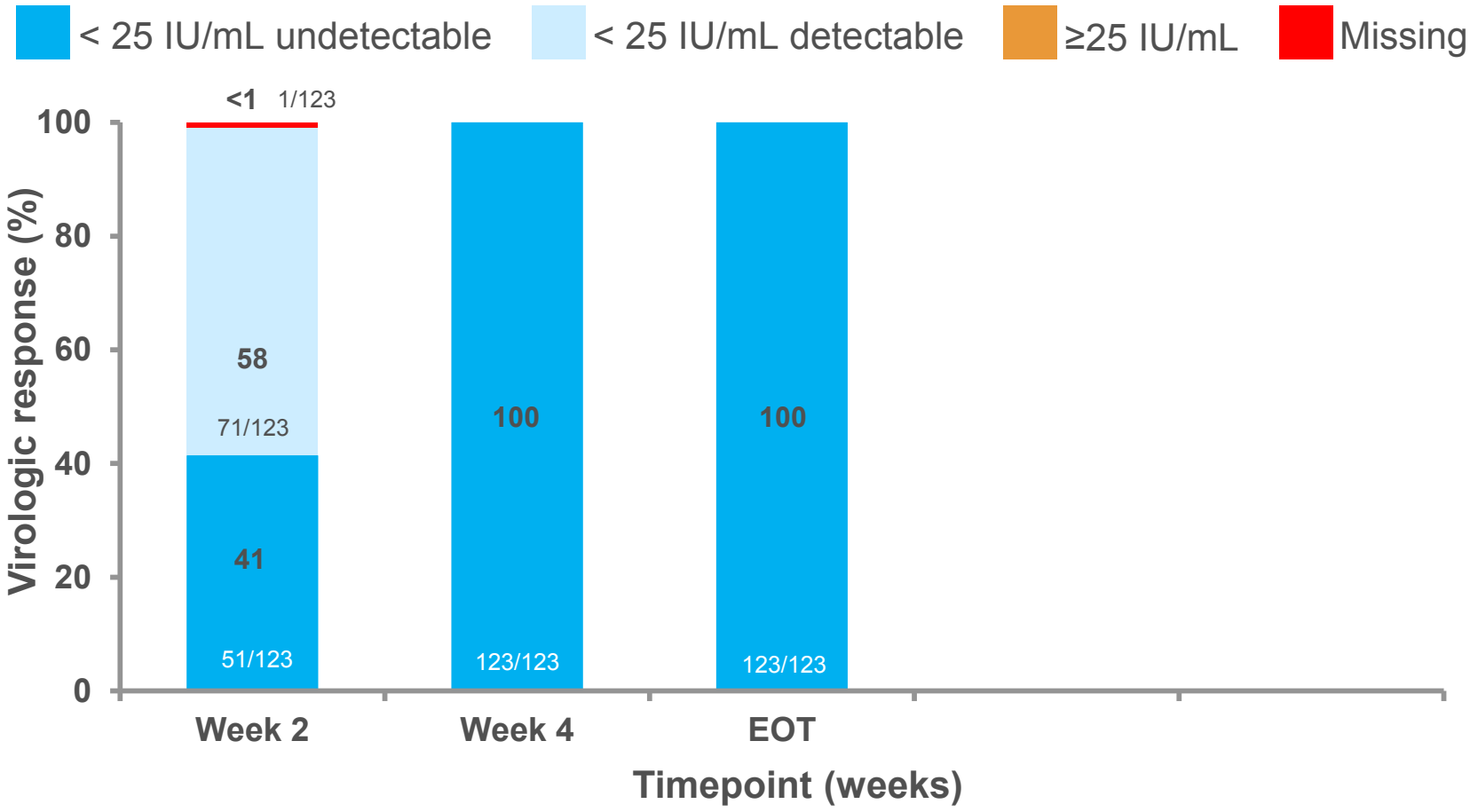
*One patient stopped both SMV and RBV (non-compliant) after RGT was determined (stopped at Week 11). The patient completed PegIFN;
‡Any patient who discontinued early and where eligibility could not be determined (n=2) was automatically included in the 24-week group
ITT: intent-to-treat; RGT: response-guided therapy

Patient demographics and disease characteristics

	12-week group (n=123)	24-week group (n=40)	Overall (N=163)
Male, n (%)	65 (53)	28 (70)	93 (57)
Age (years), median	47.0	49.5	47.0
BMI (kg/m²), median	25. 0	25.45	25.10
Race,			
White, n/N (%)	98/107 (92)	32/33 (97)	130/140 (93)
IL28B genotype, n (%)			
CC	32 (26)	8 (20)	40 (25)
CT	73 (59)	20 (50)	93 (57)
TT	18 (15)	12 (30)	30 (18)
HCV RNA (log_{10} IU/mL), median	6.26	6.62	6.35
≤800 000 IU/mL, n (%)	33 (27)	3 (8)	36 (22)
HCV genotype subtype*, n (%)			
1b	74 (60)	22 (55)	96 (59)
METAVIR score, n (%)			
F0–F1	93 (76)	25 (63)	118 (73)
F2	29 (24)	15 (38)	44 (27)

*HCV geno/subtype is based on the NS5B assay, and if not available on the LIPA HCV II or Trugene results

On-treatment response, SVR4 and SVR12 in the 12-week group



Plasma HCV RNA determined by Roche COBAS® Taqman® HCV Test v2.0 assay for use with the high pure system

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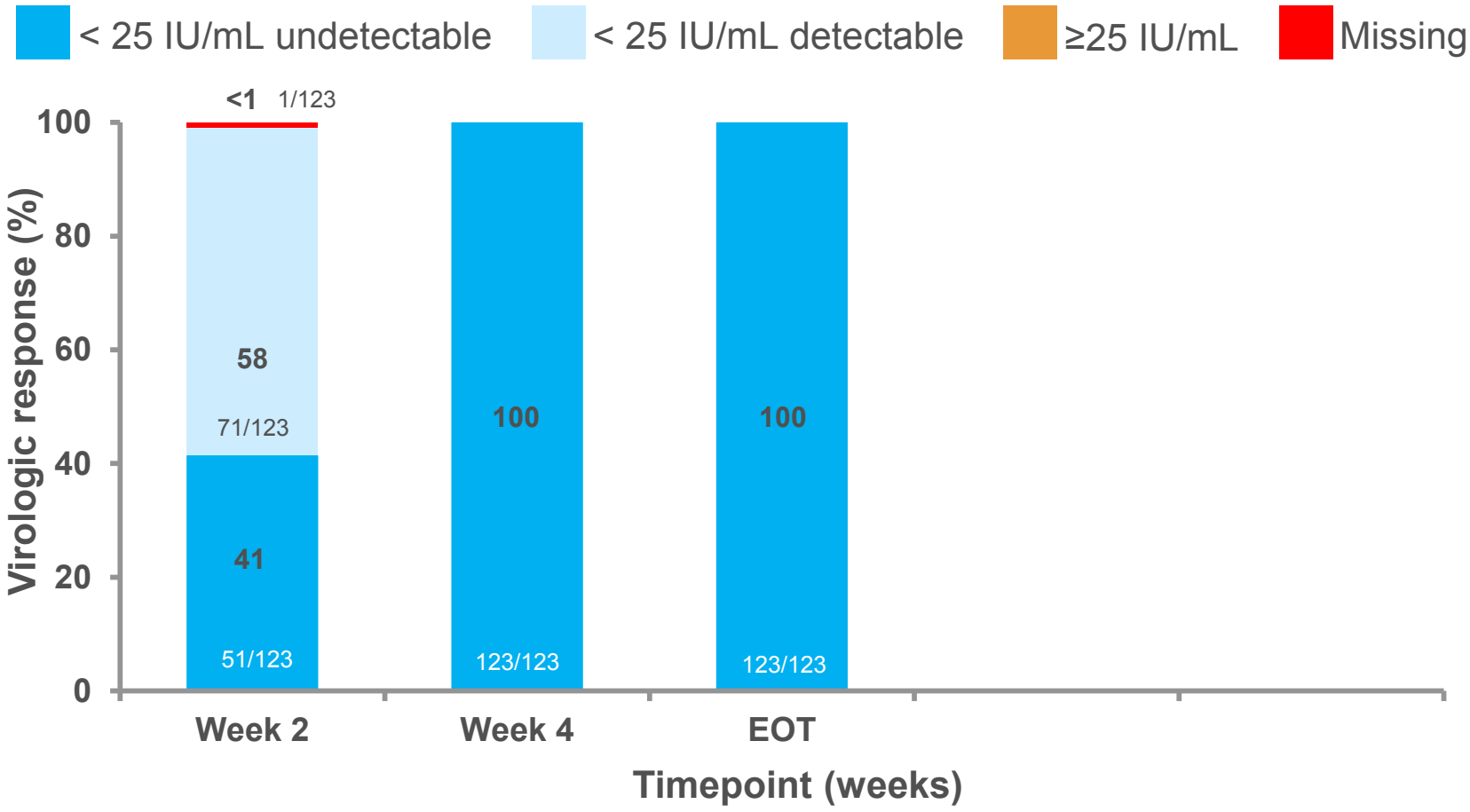

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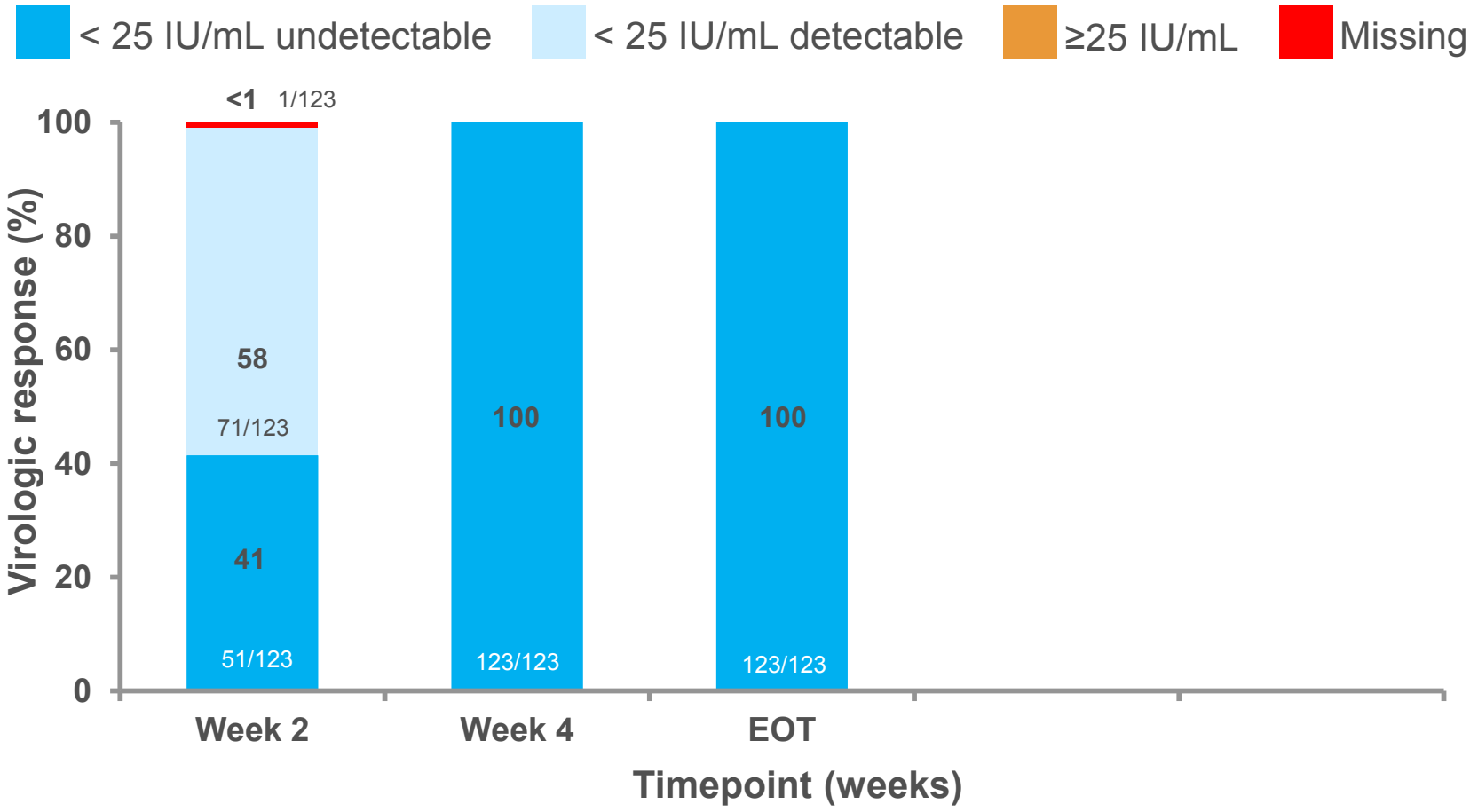

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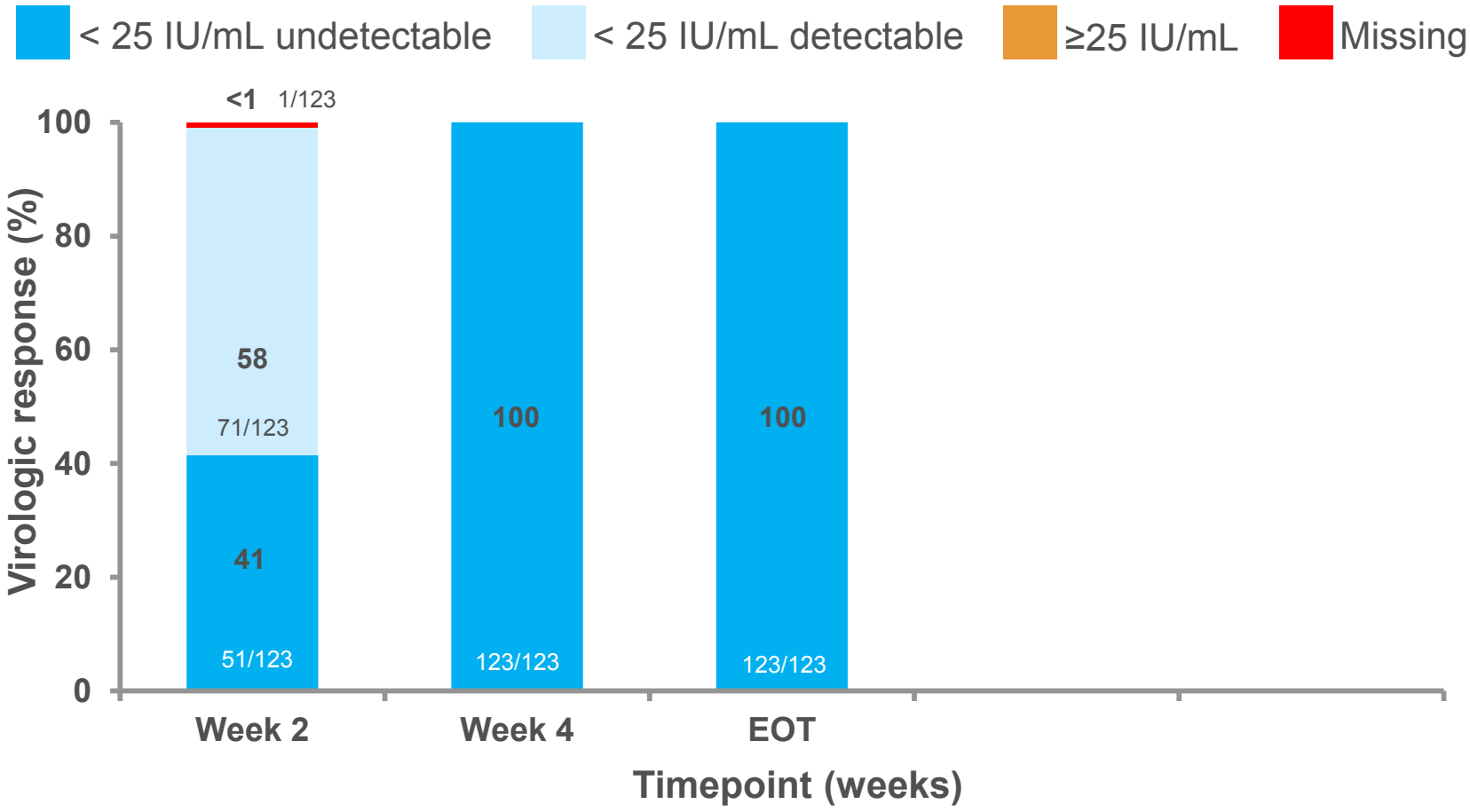

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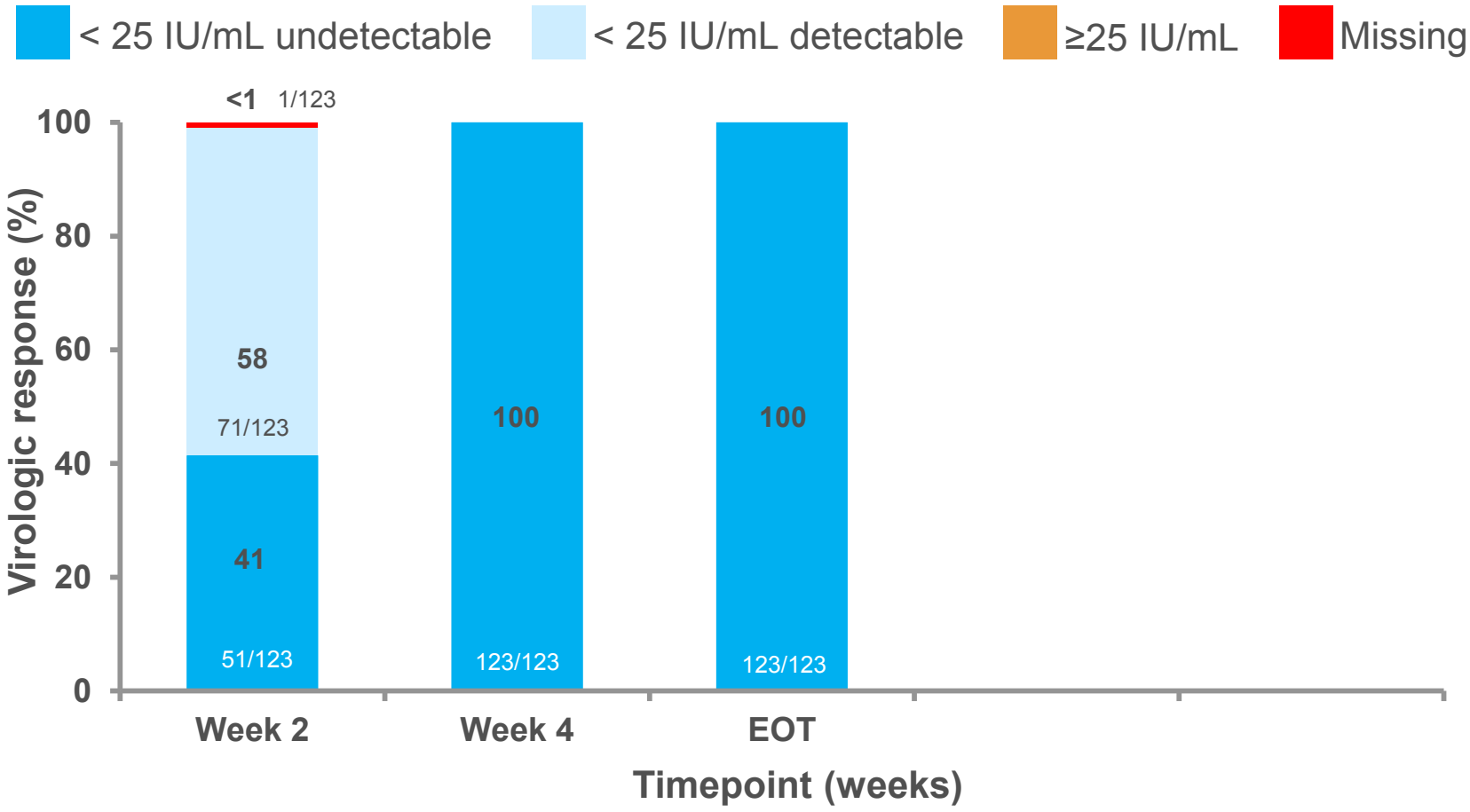

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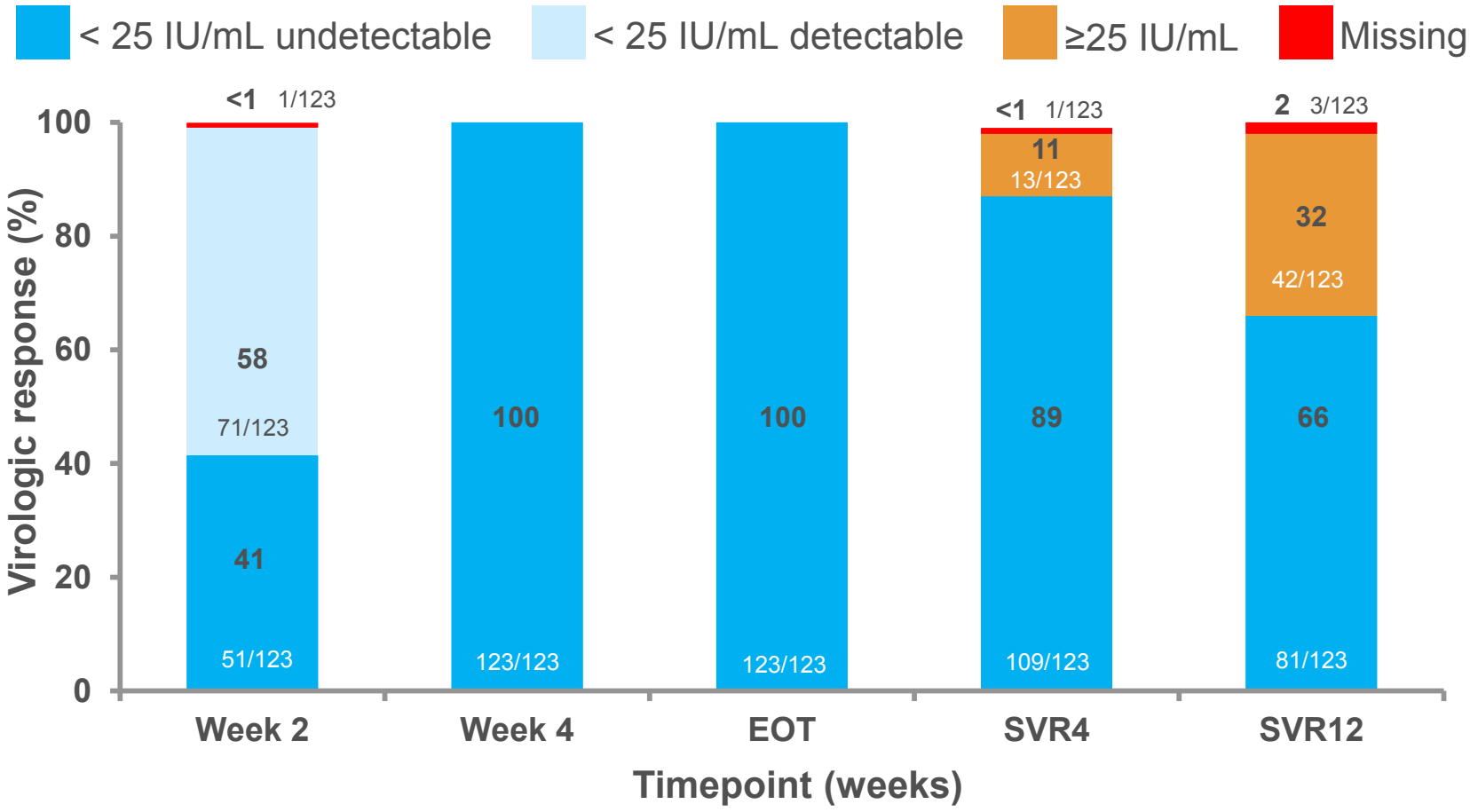

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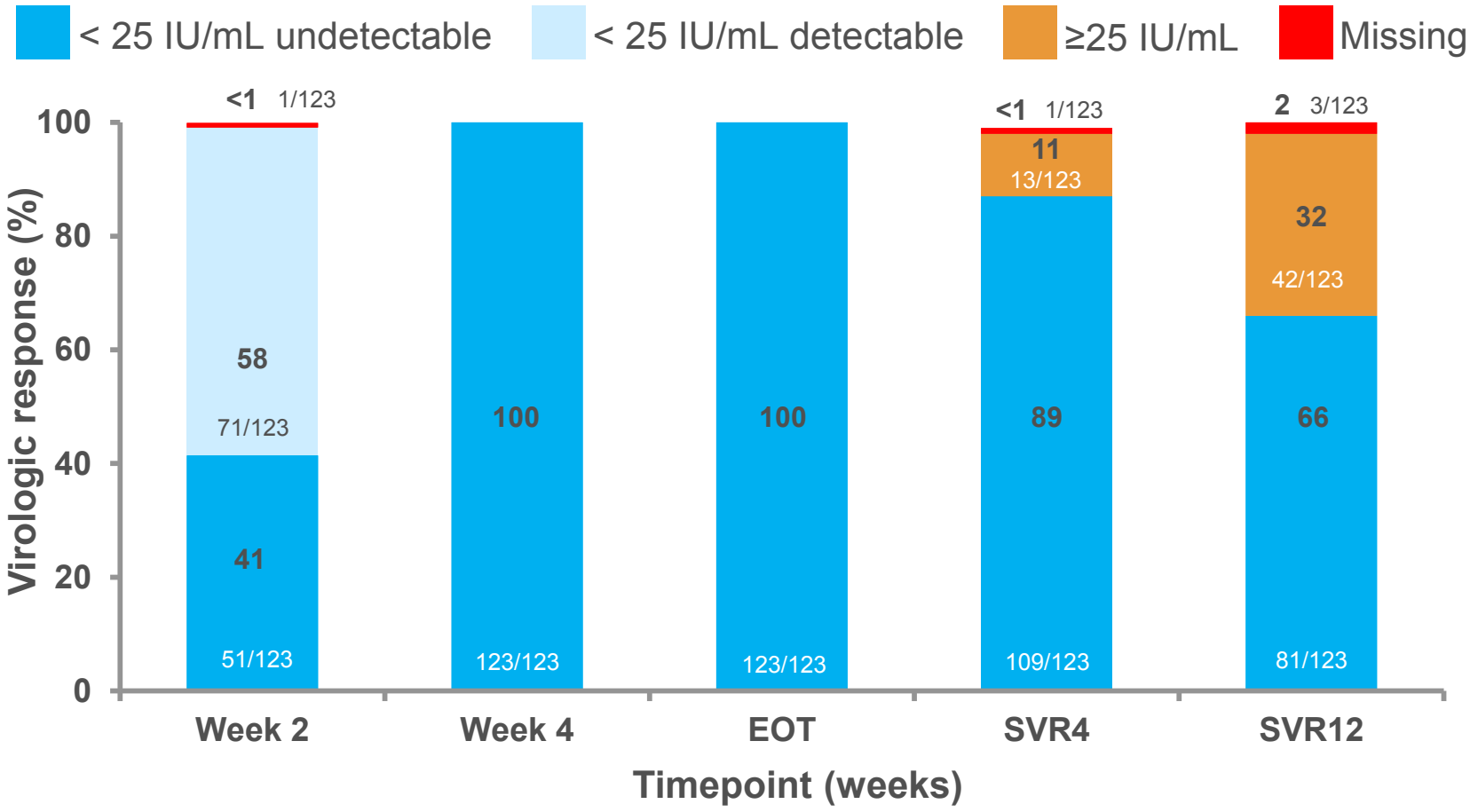

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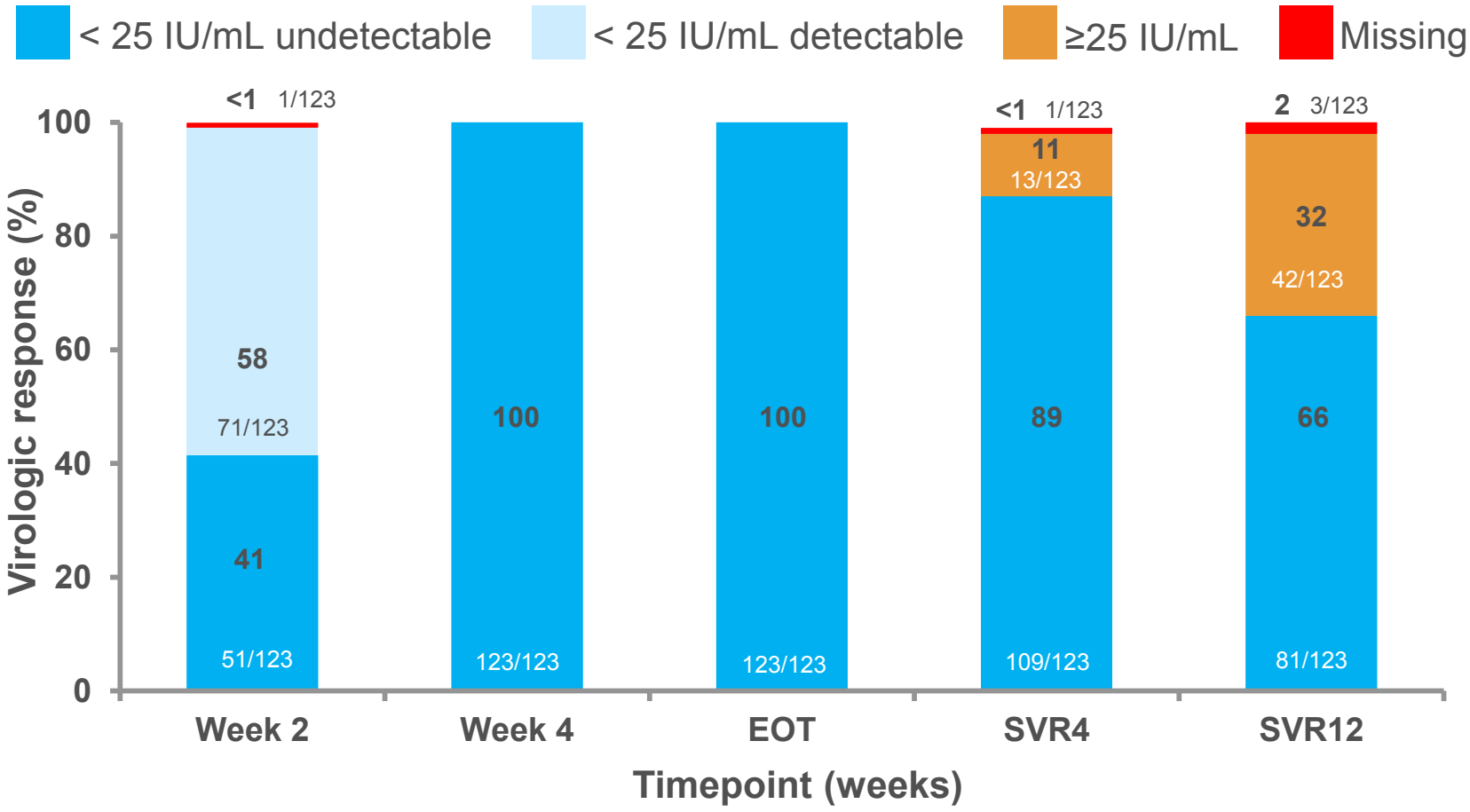

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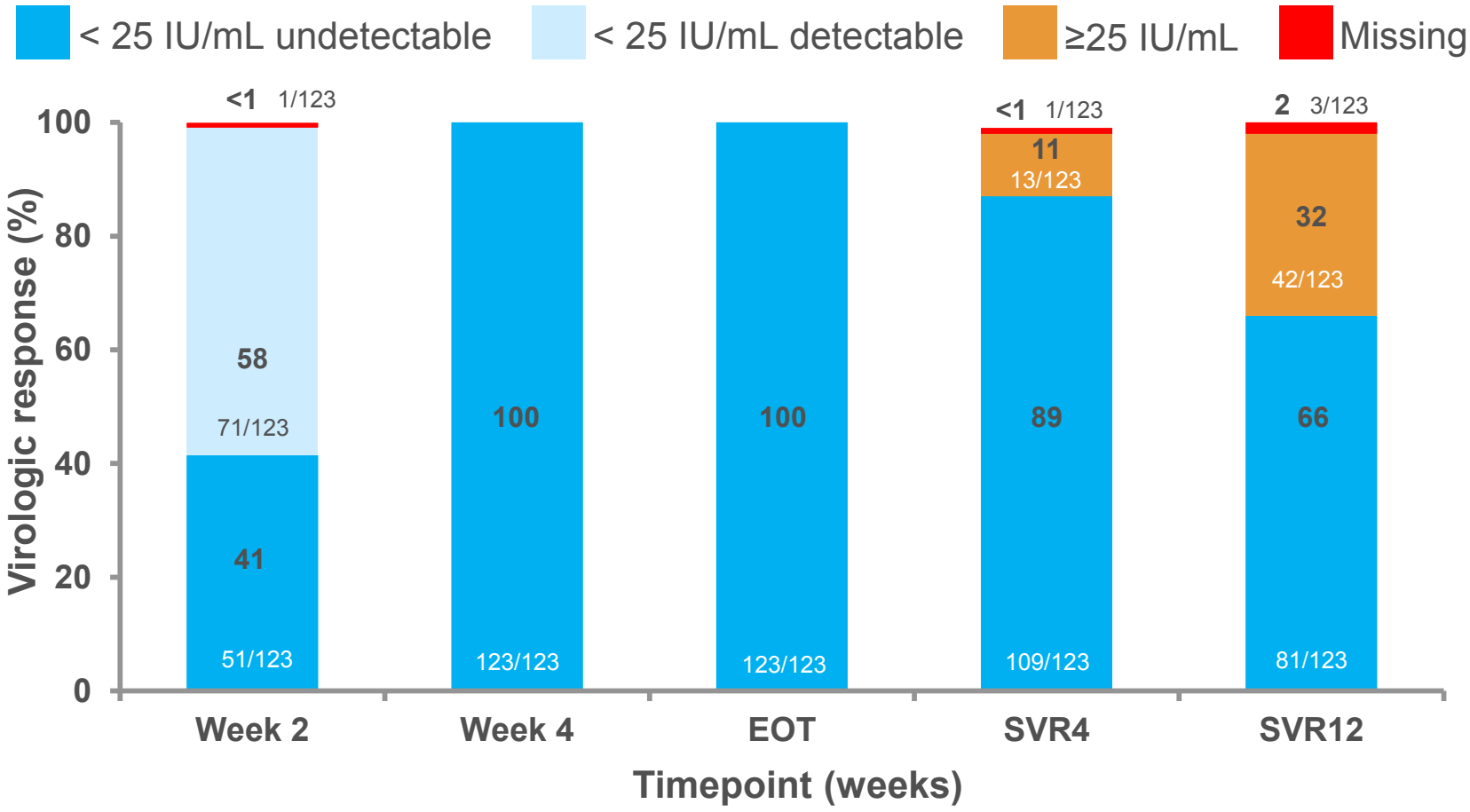

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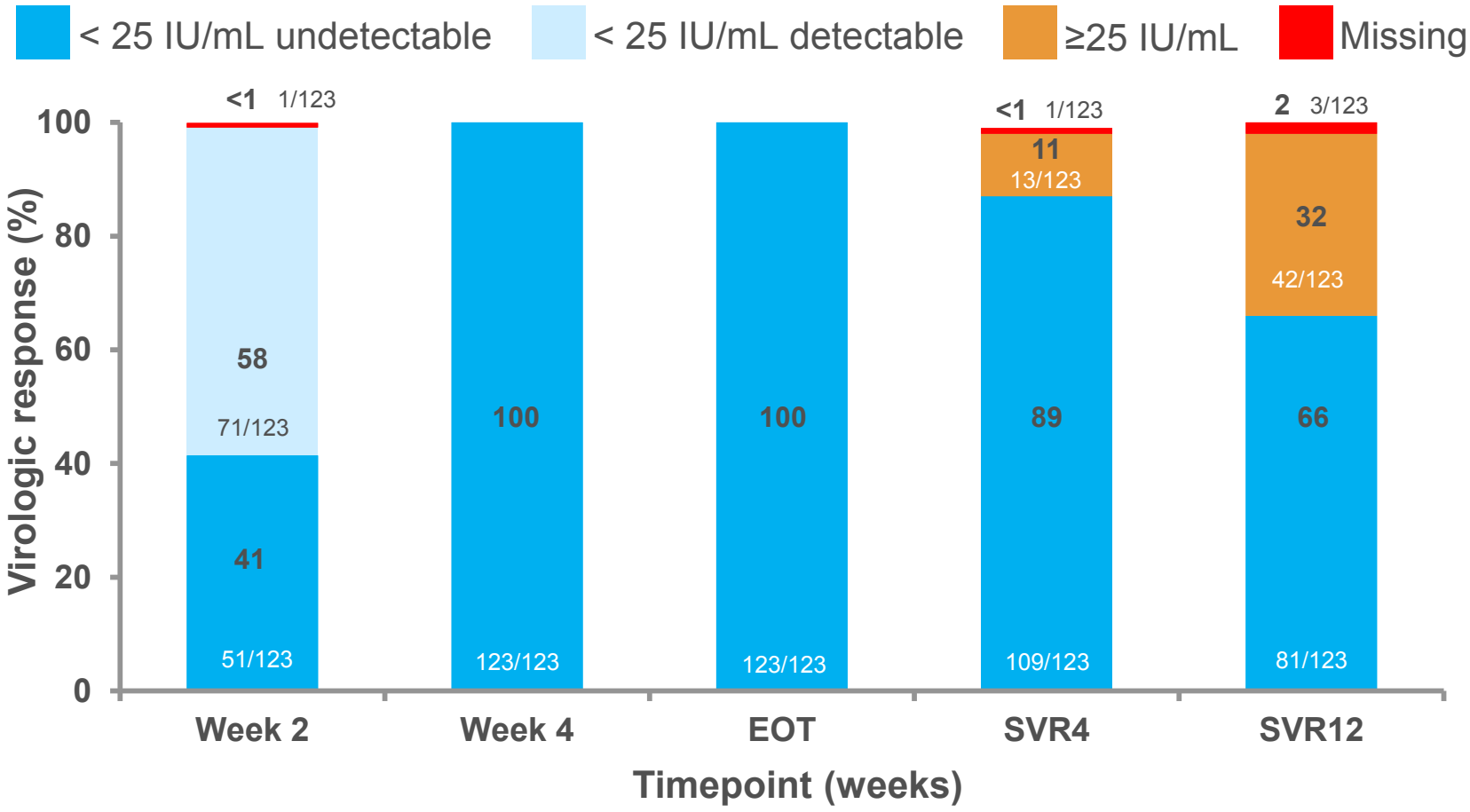

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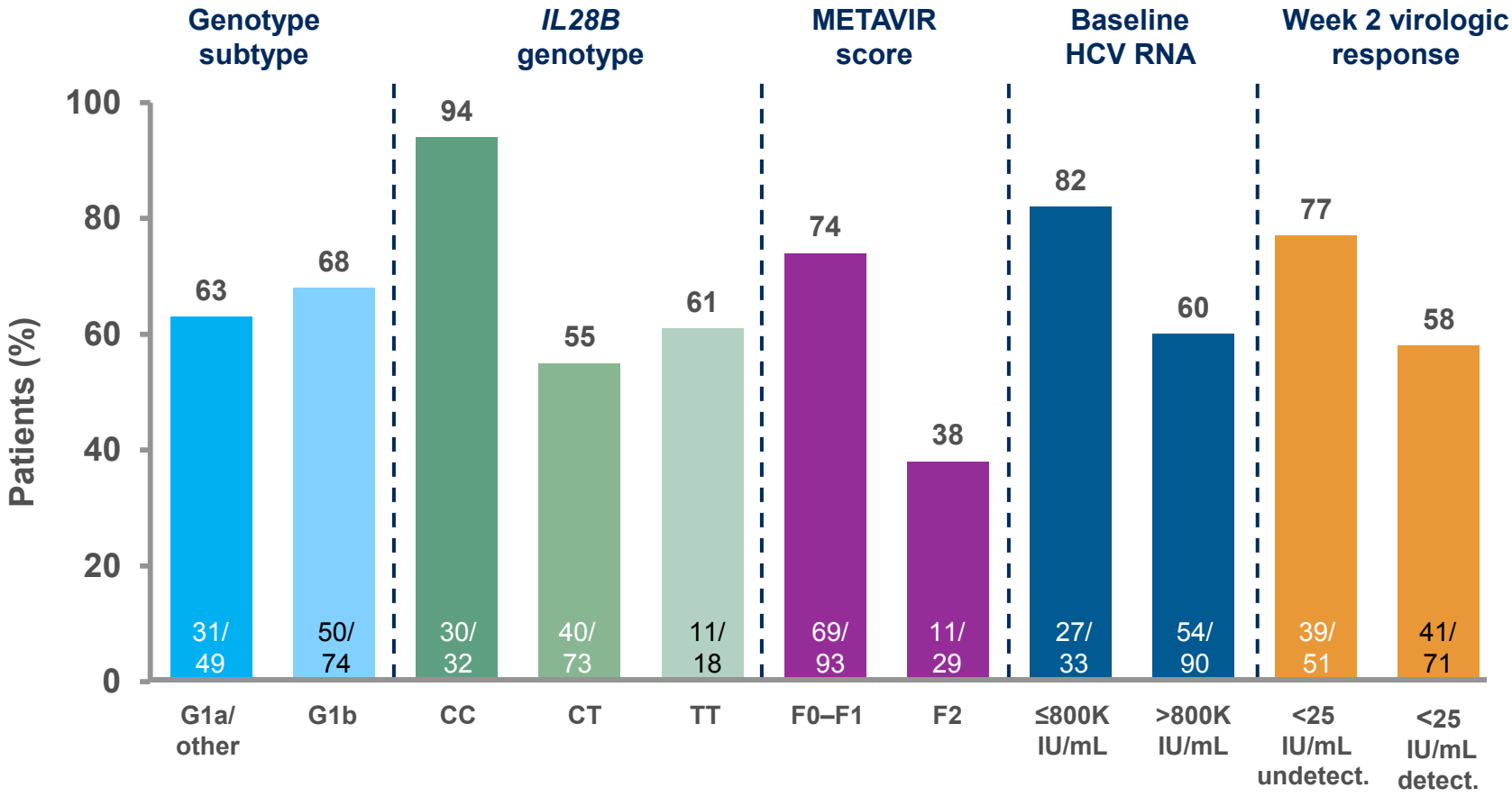
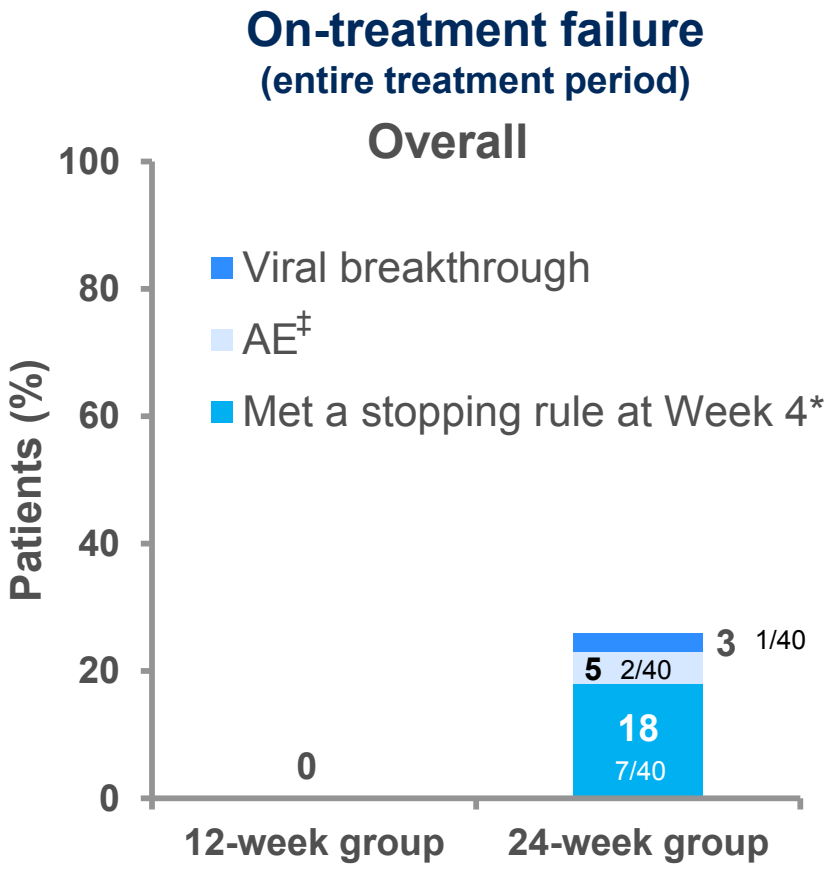
SVR12 by subgroups in the 12-week group

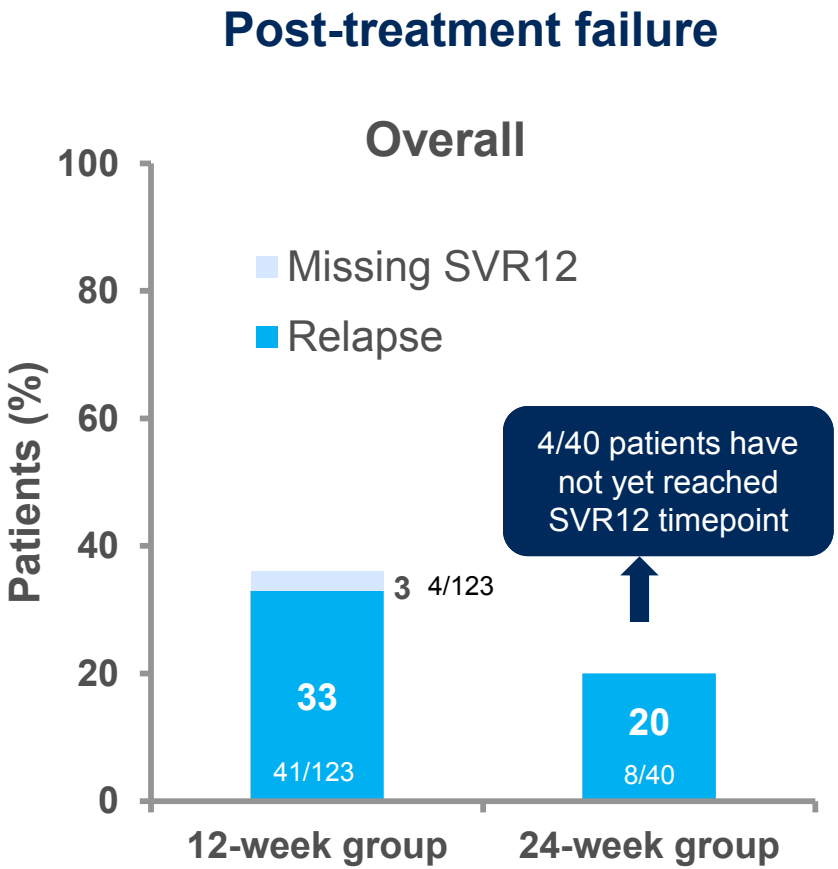


Predictors of response

- Analysis on baseline demographic and disease parameters associated with response is ongoing
- Results of a multivariate analysis show *IL28B* CC genotype, F0/F1, and low HCV RNA to be predictors of response
- Final analysis will be presented at an upcoming conference

Treatment failures by treatment group





Any patient who discontinued early and where eligibility could not be determined was automatically included in the 24-week group
*Patients stopped all therapy if HCV RNA ≥25 IU/mL at Week 4
‡Two patients withdrew due to AEs (dyspnoea and fever)

Safety: AEs by treatment group (entire treatment phase)

n (%)	12-week group (n=123)	24-week group* (n=40)	Overall (N=163)
Any AE	117 (95)	37 (93)	154 (95)
Any SAE	4 (3)	1 (3)	5 (3)
AE leading to permanent stop*	-	4 (10)	4 (3)
For all study drugs	-	3 (8)	3 (2)
For PR only	-	1 (3)	1 (1)
Worst grade 3 or 4 AE	29 (24)	8 (20)	37 (23)
Worst grade 3	23 (19)	3 (8)	26 (16)
Worst grade 4	3 (2)	3 (8)	6 (4)
At least possibly related to SMV	6 (5)	2 (5)	8 (5)
Treatment-related AE	110 (89)	36 (90)	146 (90)
At least possibly related to SMV	68 (55)	20 (50)	88 (54)

- SAEs experienced were pericoronitis, testicular necrosis, furuncle, alcohol withdrawal syndrome and rash (rash was the only AE considered possibly related to SMV)
- No grade 4 AEs were considered related to SMV; no discontinuations due to grade 3 AEs possibly related to SMV

*Results in the 24-week group are preliminary; ‡AEs leading to discontinuation in the four patients were dyspnoea (n=1), pyrexia (n=1) urinary incontinence (n=1); and rash (n=1). Rash and urinary incontinence were considered possibly related to SMV

Conclusions

- SMV + PR for 12 weeks resulted in a SVR12 rate of 66%
  - This was below the targeted 80%
- SVR rates after 12 weeks SMV + PR was not only dependent on early on-treatment response; baseline factors influenced SVR rates
  - Factors include *IL28B* genotype, fibrosis stage, baseline viral load
- Overall relapse rate in the 12-week group was 33%
  - This seemed to be driven by relapse rates in *IL28B* CT and TT patients with <25 detectable at Week 2
    - Therefore, the protocol was amended for ongoing genotype 4 patients[2]
- Ongoing analysis to predict SVR rates based on positive predictors of response identified in multivariate analysis
- Safety was comparable to other SMV + PR trials with a similar AE profile to PR alone

1. Asselah et al. EASL 2015. Poster presentation P0792
2. Asselah et al. APASL 2015. Oral presentation

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- **Robert Ryan, Oliver Lenz, Gino Van Dooren, Isabelle Lonjon-Domanec and Michael Schlag** are employees of Janssen Pharmaceuticals and may be Johnson and Johnson stockholders

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