# Direct-acting Antiviral (DAA) Regimens in Late-stage Development: Which Patients Should Wait?

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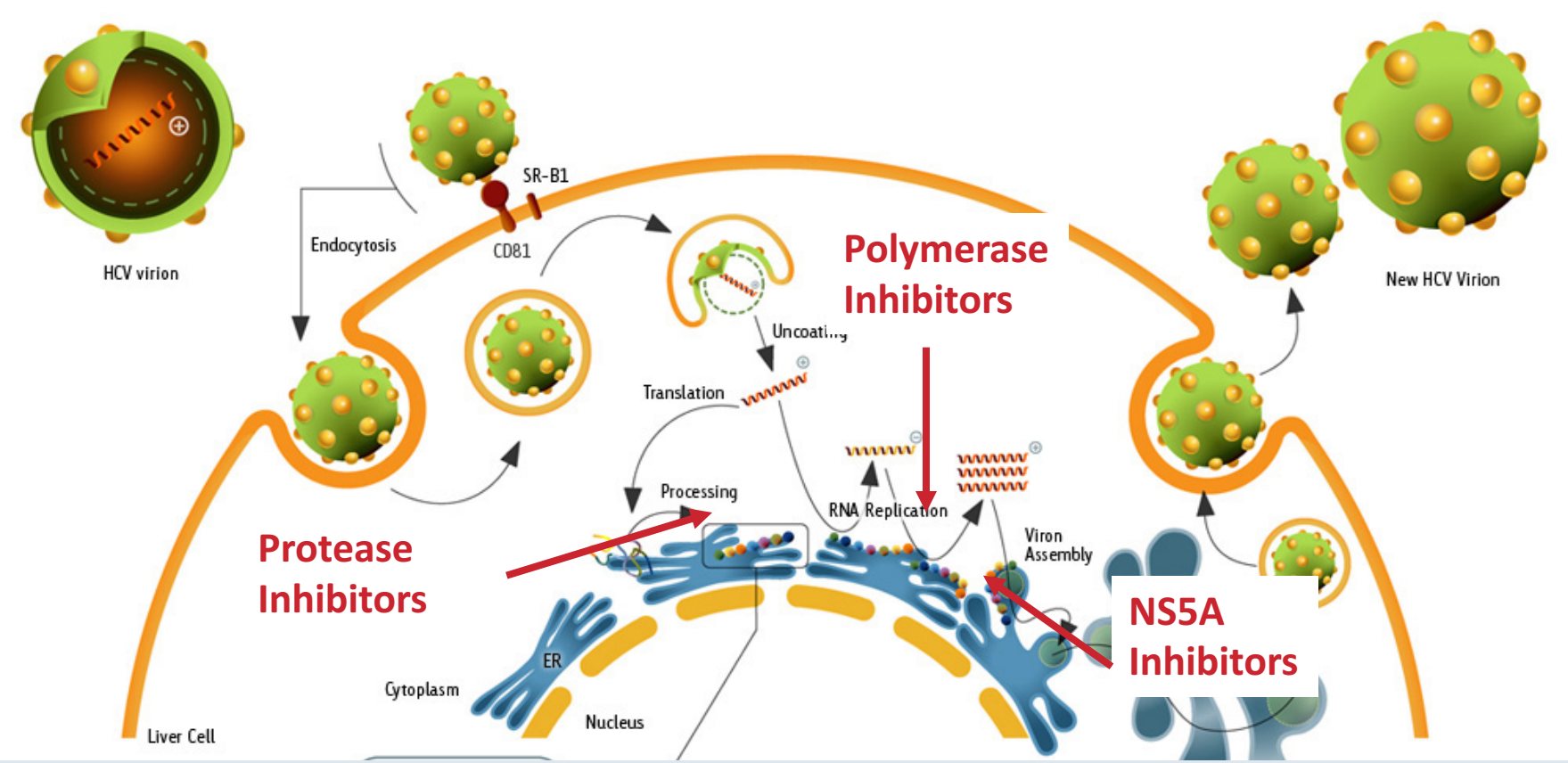
# The HCV Lifecycle: Multiple Targets




Manns. *Nat Rev.* 2007.

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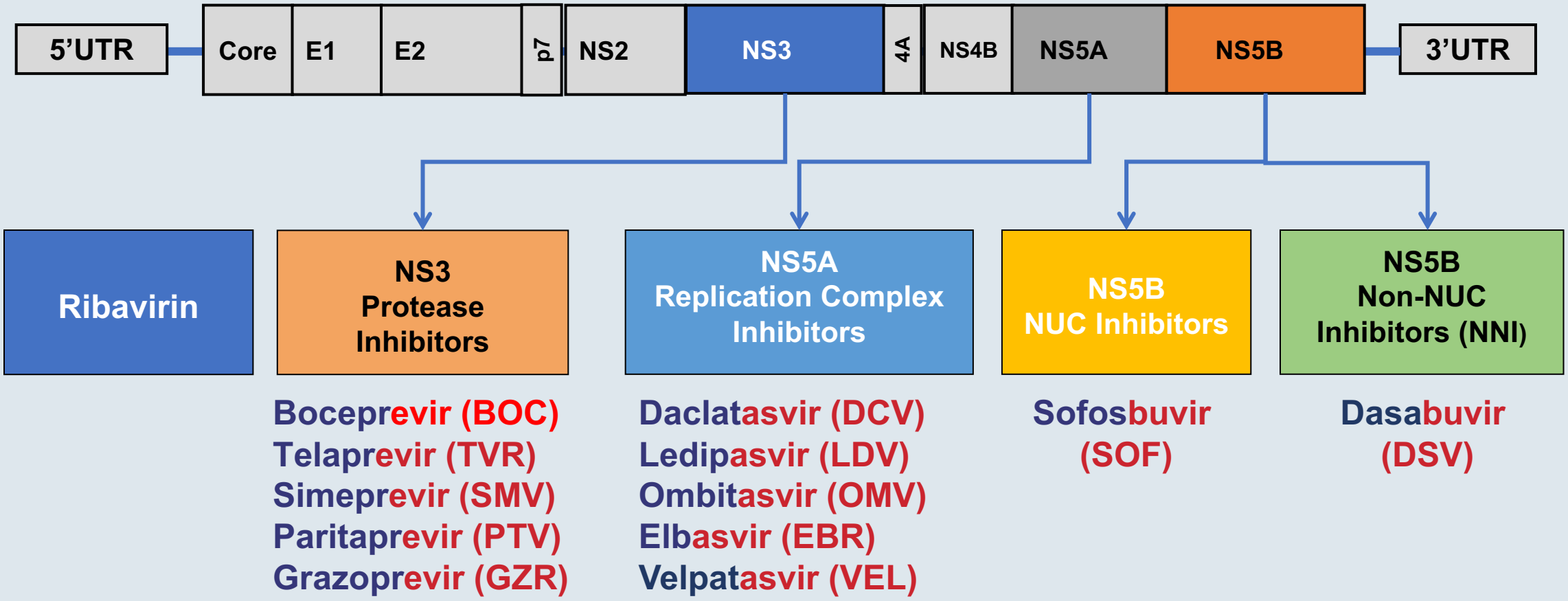
# FDA Approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes




**Note the common root name for each drug class**

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# HCV Treatment:  Innovation

- Overall, 4-5% failure rate with currently approved regimens
  - Sofosbuvir/ledipasvir
  - Paritaprevir/ritonavir/ombitasvir + dasabuvir +/- ribavirin
  - Simeprevir/sofosbuvir
  - Elbasvir/grazoprevir
  - Sofosbuvir/velpatasvir
- Very promising late-stage regimens for patients who fail current DAA therapy
  - Glecaprevir/pibrentasvir
  - Sofosbuvir/velpatasvir/voxilaprevir
  - Uprifosbuvir/grazoprevir/ruzasvir

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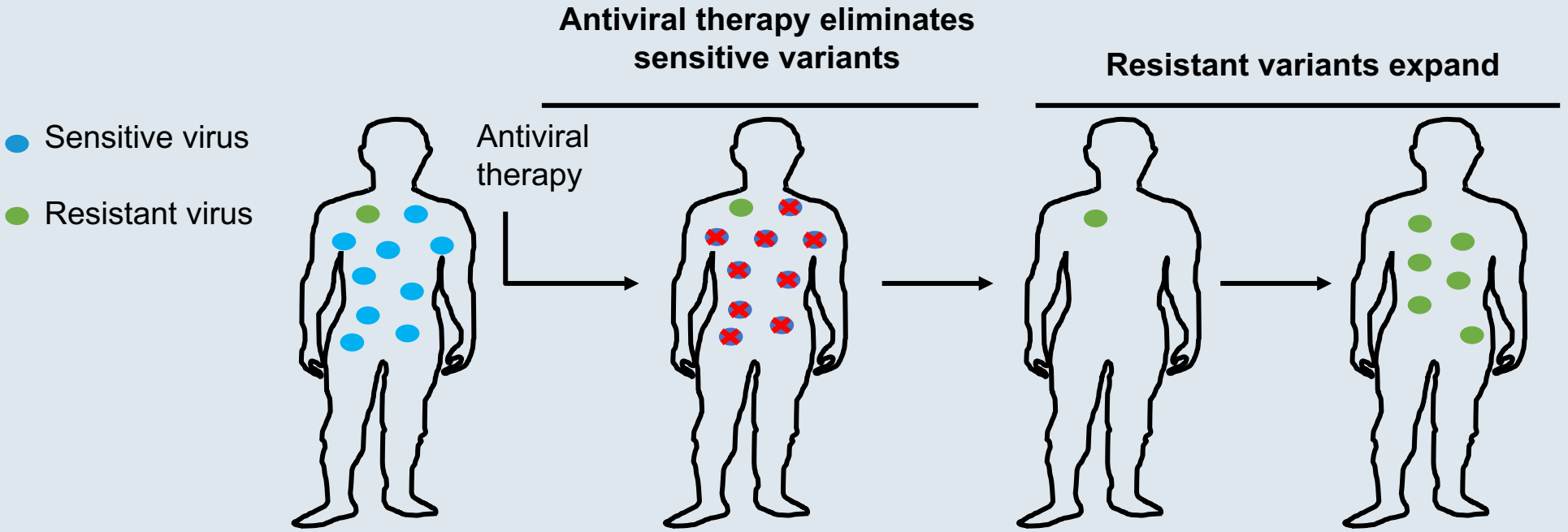
# Why Do We Need More HCV Regimens?

# Resistant Variants Are Present Before and Can Be Selected During Treatment

- HCV is a mixture of related but distinct populations of virions in each patient[1]
- Most resistant variants are unfit and may be undetectable prior to therapy[2,3]




1. Pawlotsky JM, *Clin Liver Dis*. 2003;7:45-66; 2. Kuntzen T, et al. *Hepatology*. 2008;48:1769-1778;
3. Bartels DJ, et al. *J Infect Dis*. 2008;198:800-807. Image reproduced from Forum for Collaborative HIV Research (www.hivforum.org).

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# Current and Next Generation NS3 Protease Inhibitors: Activity Against Various Subtypes *in vitro* Can Predict Lower Efficacy and Risk of RASs

| Protease Inhibitor | Stable HCV Replicon $EC_{50}$ (nM) | | | | | |
|---|---|---|---|---|---|---|
| | GT1a | GT1b | GT2a | GT3a | GT4a | GT6a |
| Glecaprevir | 0.85 | 0.94 | 2.7[a] | 1.6 | 2.8 | 0.86 |
| Paritaprevir | 1.0 | 0.21 | 5.3[a] | 19 | 0.09 | 0.68 |
| Simeprevir[1,2] | 13 | 9.4 | 15 | 472 | NA | NA |
| Asunaprevir[3] | 4.0 | 1.2 | 230 | 1162 | NA | NA |
| Grazoprevir | 0.38 | 0.87 | 1.3 | 36 | 1.2 | 0.89 |
| Voxilaprevir[4] | 3.9 | 3.3 | 3.7 | 6.1 | 2.9 | 1.5 |

[a]Study conducted at Southern Research Institute.
NA, not available.

Those in red are components of next generation DAA regimens

1. Simeprevir prescribing information; 2. Chase R, et al. IAPAC, 2013; 3.McPhee F, et al. AAC, 2012; 4. Taylor J, et al. EASL, 2015. Poordad, et al. Abstract #41, AASLD 2015.

# NS5A Inhibitors: Activity Against Various Subtypes *in vitro* Can Predict Lower Efficacy and Risk of RASs (Those in red are components of next generation DAA regimens)

| NS5A Inhibitor | Stable HCV Replicon $EC_{50}$ (pM) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | GT1a | GT1b | GT2a | GT2b | GT3a | GT4a | GT5a | GT6a |
| Pibrentasvir | 2 | 4 | 2[a] | 2 | 2 | 2 | 1 | 3 |
| Ombitasvir | 14 | 5 | 12 | 4 | 19 | 2 | 3 | 366 |
| Daclatasvir[1] | 22 | 3 | 13,000 | NA | 530 | 13 | 5 | 74 |
| Ledipasvir[2] | 31 | 4 | 21,000 | 16,000 | 168,000 | 390 | 150 | 1100 |
| Velpatasvir[3] | 12 | 15 | 9 | 8 | 12 | 9 | 75 | 6 |
| Elbasvir[4] | 4 | 3 | 3 | 3000 | 20 | 3 | 1 | 3 |
| Ruzasvir[5] | 1 | 2 | 1 | 4 | 2 | 2 | 1 | 4 |
| ACH-3102[6] | 26 | 5 | 21 | ~150 | NA | NA | NA | NA |
| IDX719[7] | 8 | 3 | 24 | NA | 17 | 2 | 37 | NA |

[a]Study conducted at Southern Research Institute.
NA, not available.


1. Wang C, et al. AAC, 2014
2. Cheng G, et al. EASL, 2012; Harvoni prescribing information.
3. Cheng G, et al. EASL, 2013
4. Liu R, et al. EASL, 2012
5. Asante-Appiah E, AASLD, 2014
6. Zhao Y, et al. EASL, 2012
7. Dousson C, et al. EASL, 2011

# NS5A Resistance Overview

- Baseline variants associated with resistance are relatively prevalent
  - 15-20% of patients who have never been treated with HCV DAAs have them
- Currently available NS5A inhibitors suffer from broad cross-resistance at key positions
  - Q30R, L31M/V, Y93H/N
- NS5A variants persist for prolonged periods
- Select NS5A RAVs impact re-treatment responses

# HCV Treatment:  Current Challenges

- Failures with NS5A substitutions
  - Present in >80% of patients prior to retreatment
  - ≥95% SVR12 attained when retreating with regimens in late stage development
  - Fail with a similar resistance profile
  - Currently, we can treat all patients since salvage therapies will be available in the near future

# DAA Regimens in Late-stage Development (Some Highlights)

# Glecaprevir (GLE)(ABT-493)/Pibrentasvir (PIB) (ABT-530): Known as G/P

**Glecaprevir**
**(formerly ABT-493)**
pangenotypic NS3/4A protease inhibitor


Collectively: G/P

**Pibrentasvir**
**(formerly ABT-530)**
pangenotypic NS5A inhibitor

**In vitro:**[1,2]

- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

**Clinical PK & metabolism:**

- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%); no dose adjustment for CKD[3]

1. Ng TI, et al. Abstract 636. CROI, 2014; 2. Ng TI, et al. Abstract 639. CROI, 2014; 3. Kosloski M, et al. Abstract THU-230. EASL 2016.
G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg

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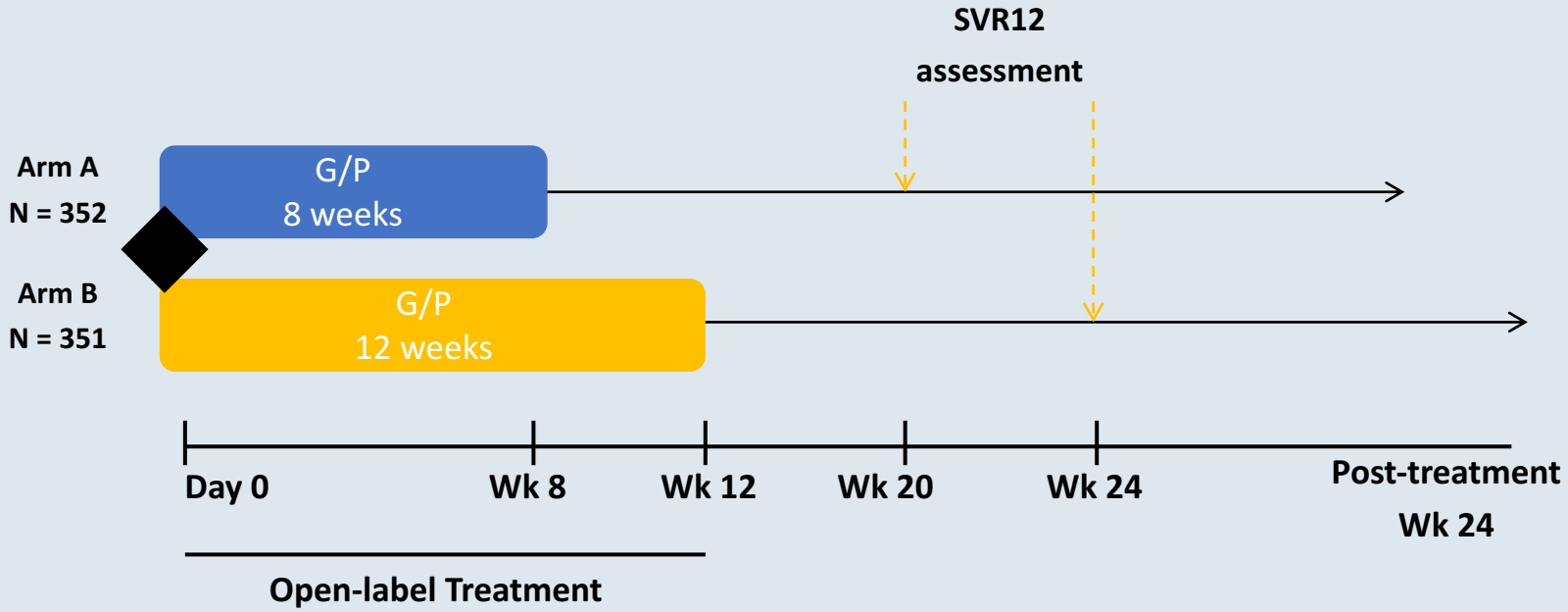
# ENDURANCE-1 (GLE/PIB): Study Design and Patient Population




- GT1 non-cirrhotics (n=703)
- Treatment naïve or treatment-experienced with IFN or PEG +/- RBV or SOF + RBV +/- PEG (excluded any prior experience with HCV DAA other than SOF)
- HCV monoinfected or HCV/HIV coinfected (ART naïve or on stable ART regimen)

Zeuzem S, et al. Abstract #253, AASLD 2016.

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# ENDURANCE-1: Baseline Variants (Never Previously Exposed to an NS5A DAA)

| Sequence, n (%) | 8-week N=331 | 12-week N=336 |
|---|---|---|
| **None** | 236 (71) | 244 (73) |
| **NS3 Only** | 4 (1) | 1 (0.3) |
| **NS5A Only** | 89 (27) | 91 (27) |
| **NS3 + NS5A** | 2 (0.6) | 0 |

Zeuzem S, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 253.

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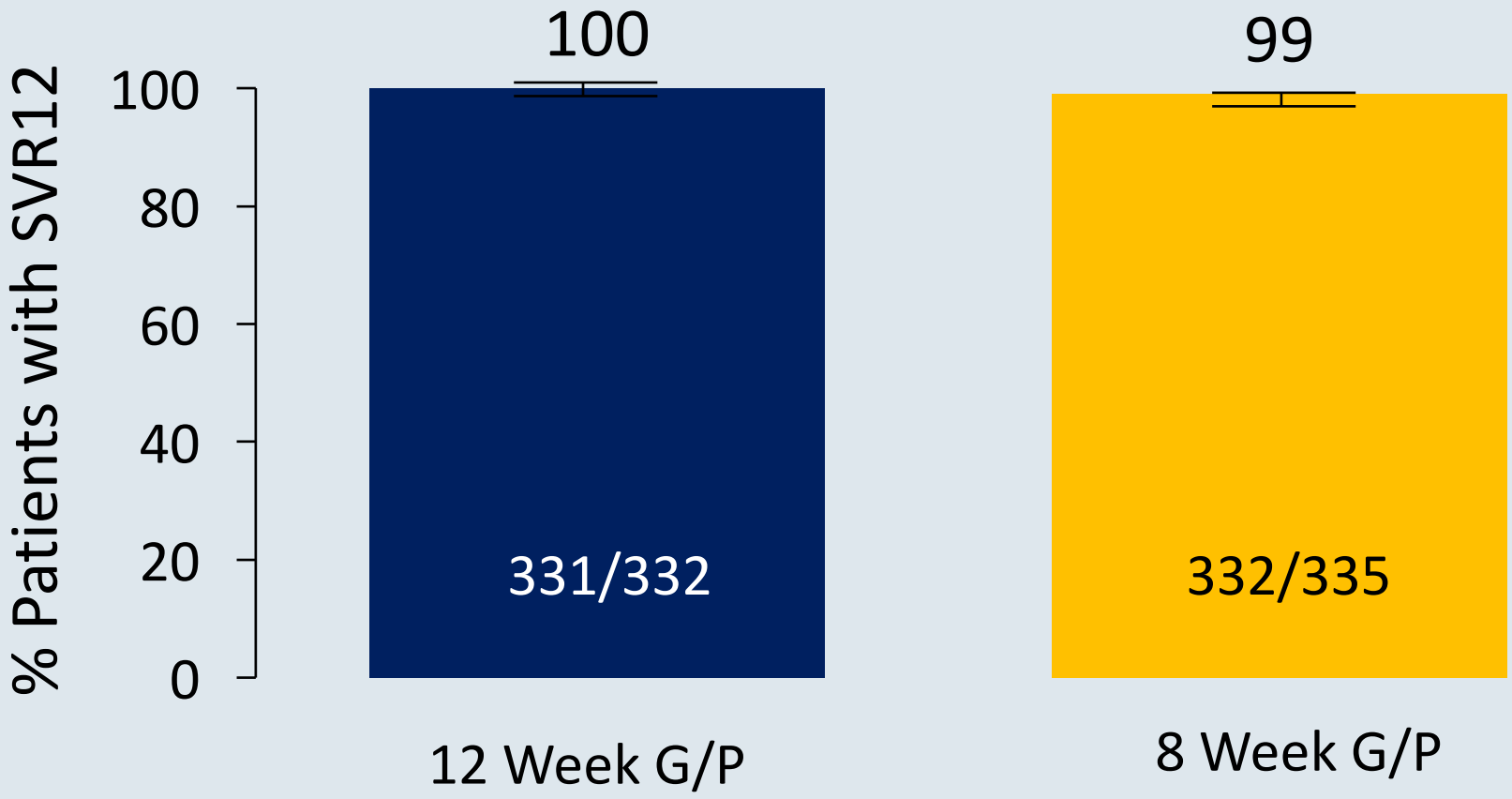
# GLE/PIB x 8 Weeks or 12 Weeks in GT1 Noncirrhotics




Zeuzem S, et al. Abstract #253, AASLD 2016.

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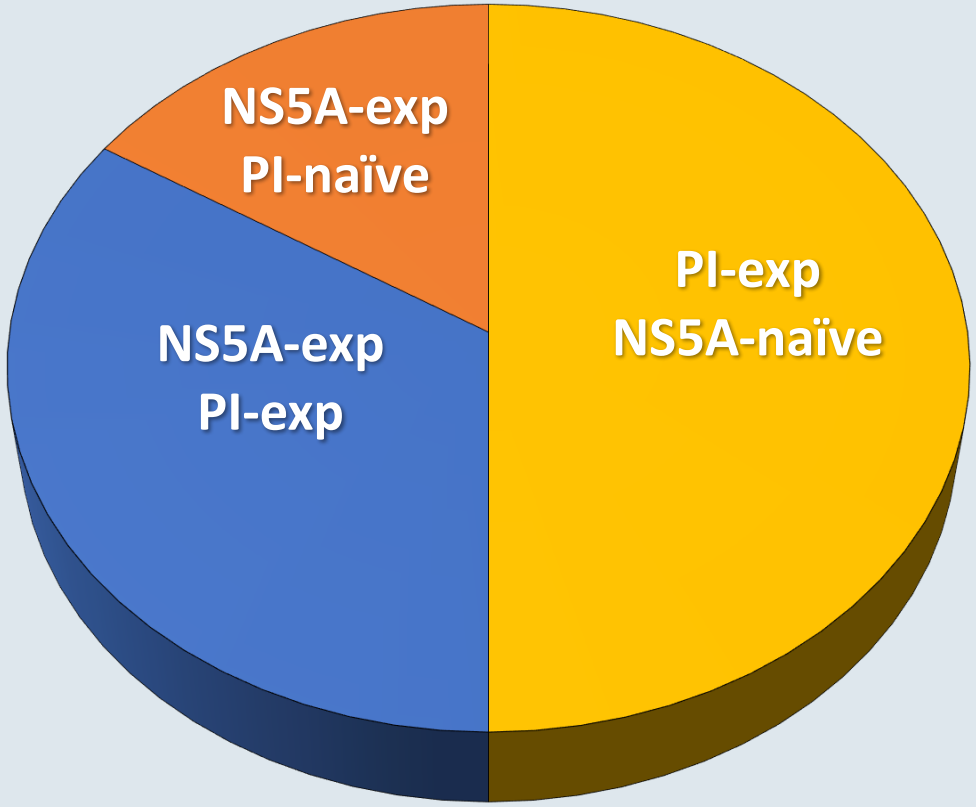
# MAGELLAN-1 Study: DAA Failure Retreatment

| Prior regimen | n |
|---|---|
| LDV/SOF | 8 |
| SMV + SOF ± RBV | 8 |
| OBV/PTV/r + DSV ± RBV | 4 |
| DBV + FDV + RDV ± RBV | 4 |
| SAM + SMV | 2 |
| TVR + PR | 8 |
| BOC + PR | 10 |
| DCV ± PR | 2 |
| Other | 9 |
| 4 patients were treated more than once with DAA-containing regimens. | |

Treatment experience by DAA class:




25 (50%) NS5A-experienced
42 (84%) PI-experienced

Poordad F, et al. Abstract #GS11, EASL 2016.

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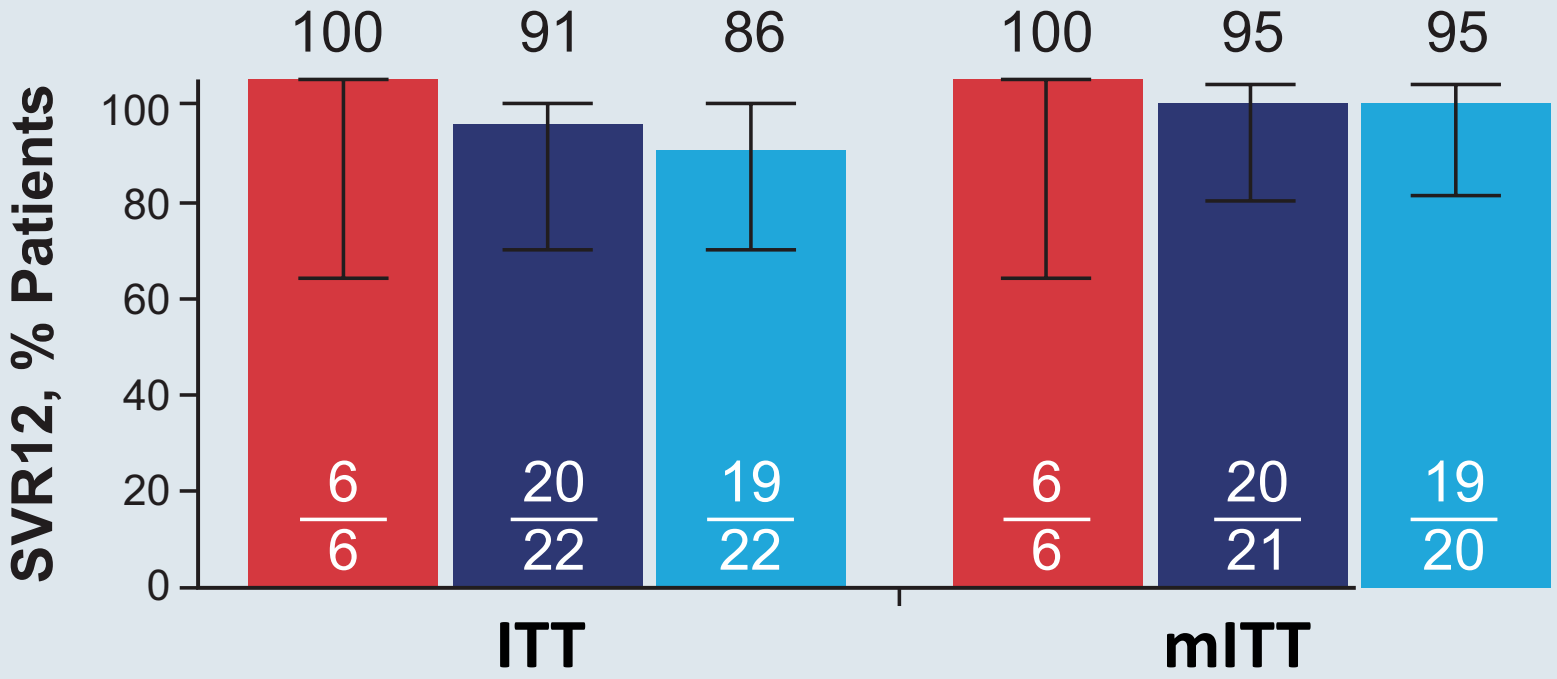
# MAGELLAN-1: SVR12




| | | | | | | |
|---|---|---|---|---|---|---|
| **ABT-493** | **200** | **300** | **300** | **200** | **300** | **300** |
| **ABT-530** | **120** | **120** | **120** | **120** | **120** | **120** |
| **RBV** | | **800** | | | **800** | |
| **Breakthrough** | **0** | **0** | **1** | **0** | **0** | **1** |
| **Relapse** | **0** | **1** | **0** | **0** | **1** | **0** |
| **LTFU** | **0** | **1** | **2** | **--** | **--** | **--** |

1 LTFU after week 6 with HCV RNA undetectable

2 patients LTFU after completing treatment (1 death); both achieved SVR8

Poordad F, et al. Abstract #GS11, EASL 2016.

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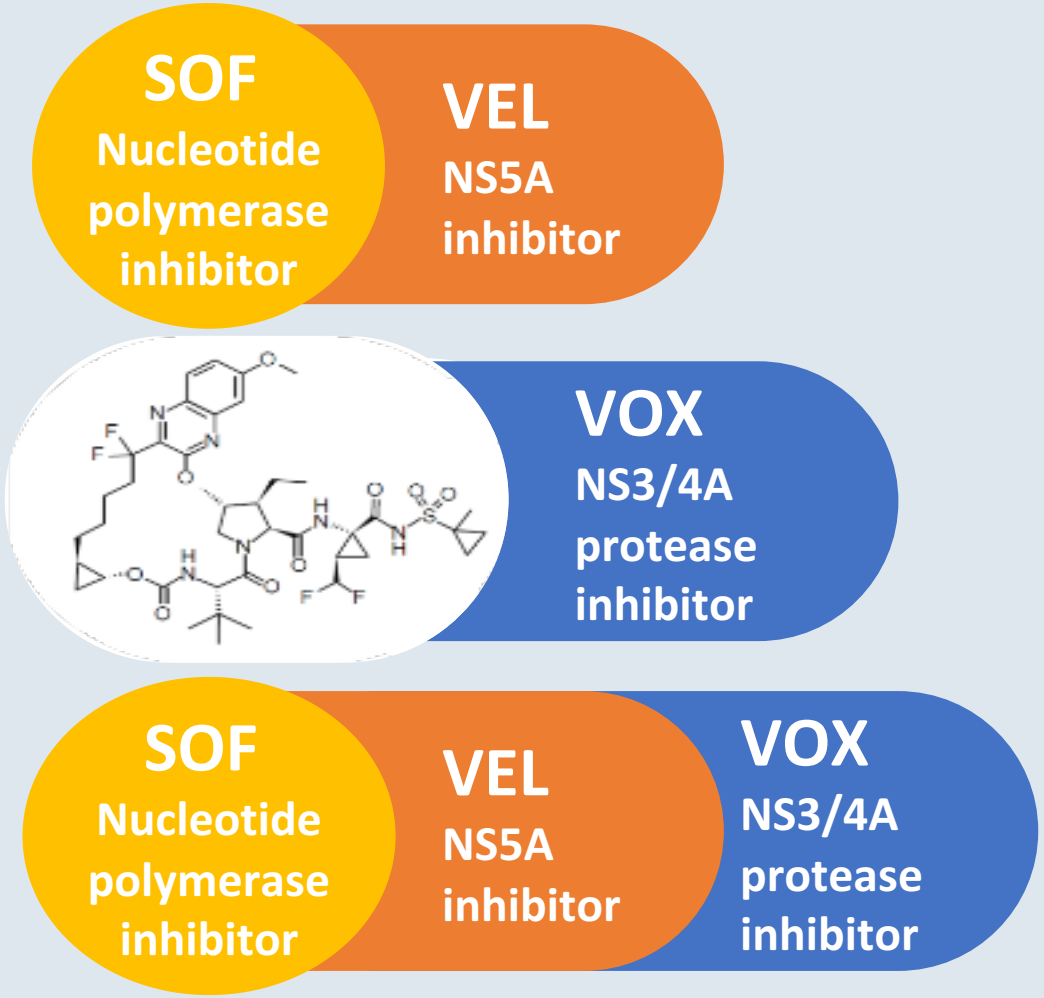
# Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX)




**Sofosbuvir (SOF)/Velpatasvir (VEL)**

- **SOF:** Nucleoside polymerase inhibitor with activity against HCV GT 1-6
- **VEL:** Potent pangenotypic NS5A inhibitor

**Voxilaprevir (VOX)**

- HCV NS3/4A PI with potent antiviral activity against GT 1-6, including most RASs

**SOF/VEL/VOX**

- Once daily, oral, fixed-dose combination (400/100/100 mg) for GT 1-6

Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

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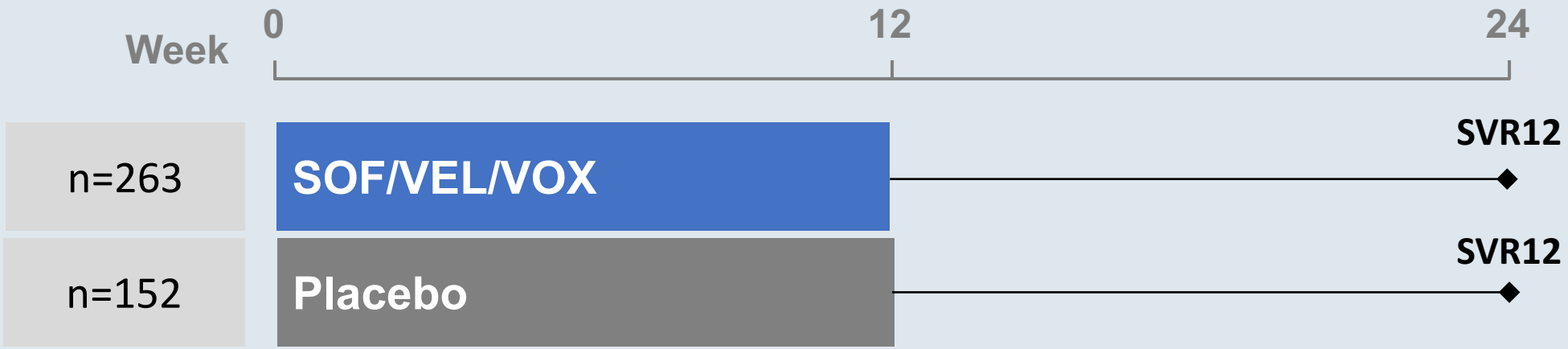
# POLARIS-1: SOF/VEL/VOX as a Salvage Regimen in NS5A Experienced Patients with GT1 - 6




- Double-blind, randomized, placebo-controlled trial in NS5A-experienced GT 1–6 patients conducted at 109 sites (USA, Canada, France, Germany, UK, Australia, New Zealand)

Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

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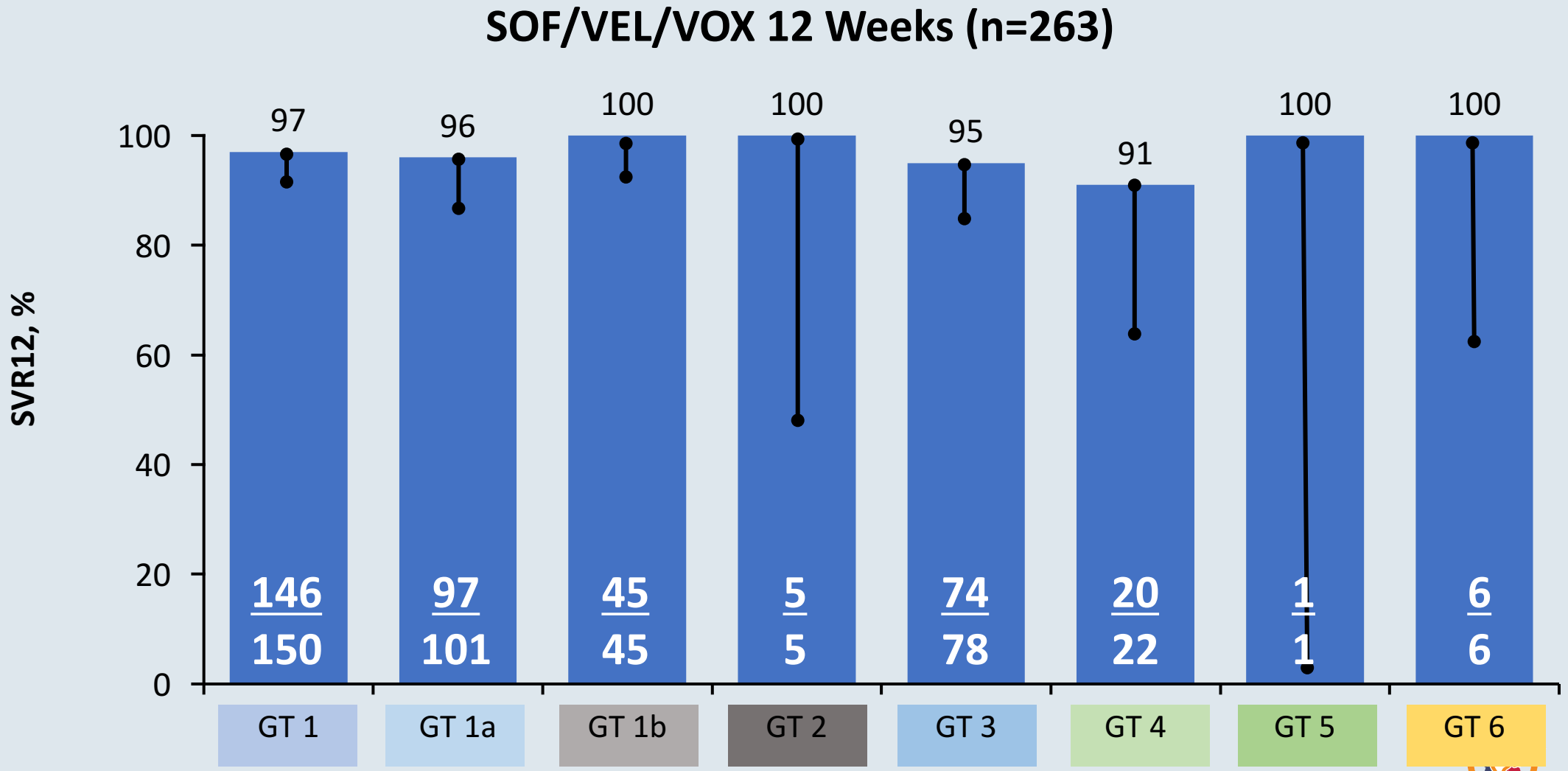
# POLARIS-1 Study:
# SVR12 by Subtype/Genotype




Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

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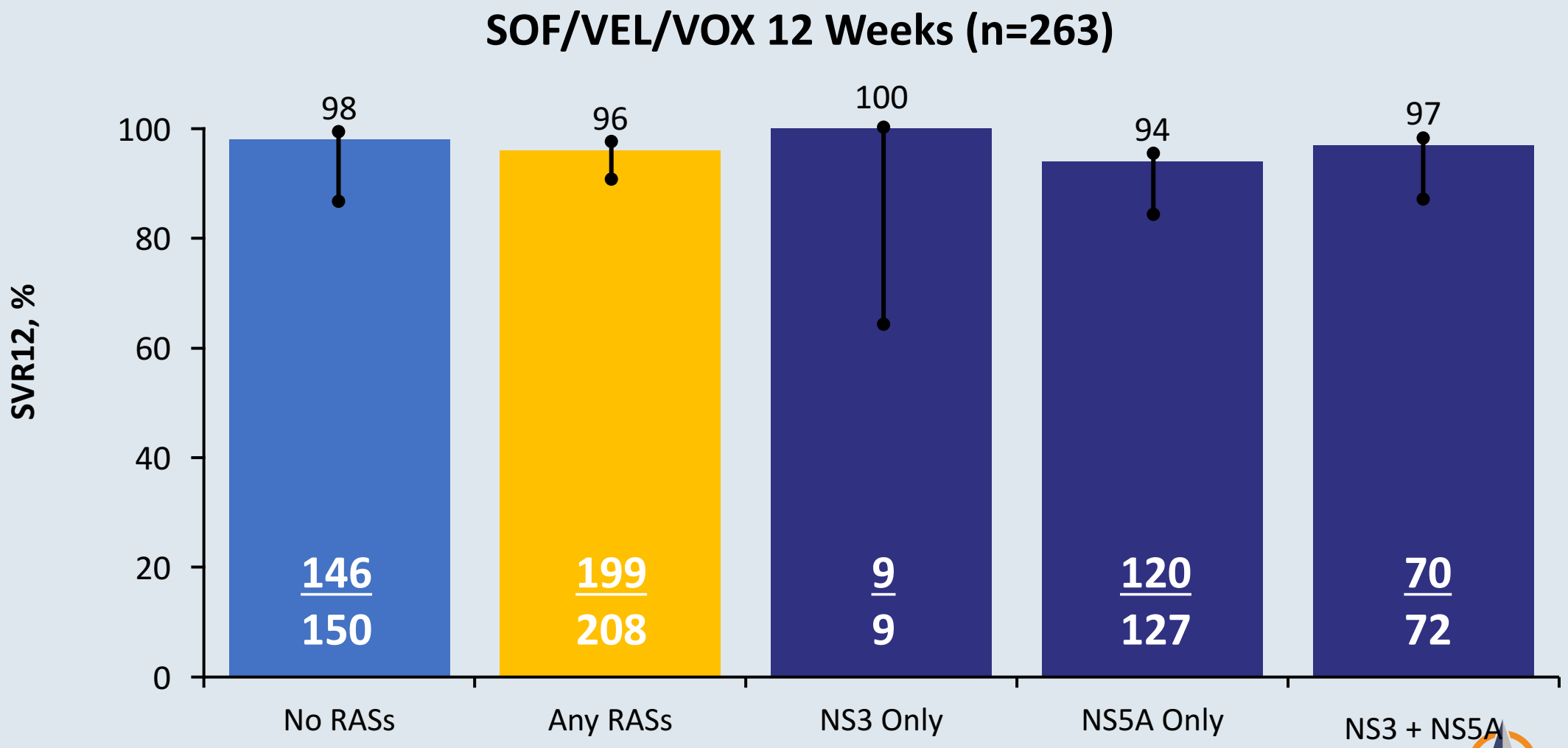
# POLARIS-1: SVR12 by RAS Status




Two patients had S282T at baseline, both achieved SVR12

Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

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# POLARIS-2: Randomized Controlled Trial of SOF/VEL/VOX for 8 Weeks versus SOF/VEL for 12 Weeks

- Open-label
- Treatment-naïve and experienced (interferon/ribavirin only)

| | | SOF/VEL/VOX 8 Weeks n=501 | SOF/VEL 12 Weeks n=440 |
|---|---|---|---|
| Mean age, y (range) | | 53 (18–78) | 52 (19–82) |
| Male, n (%) | | 255 (51) | 237 (54) |
| White, n (%) | | 391 (78) | 365 (83) |
| Mean BMI, kg/m$^2$ (range) | | 27 (17–57) | 27 (18–54) |
| Cirrhosis, n (%) | | 90 (18) | 84 (19) |
| Genotype, n (%)* | 1a / 1b / Other | 169 (34) / 63 (13) / 1 (<1) | 172 (39) / 59 (13) / 1 (<1) |
| | 2 | 63 (13) | 53 (12) |
| | 3 | 92 (18) | 89 (20) |
| | 4 | 63 (13) | 57 (13) |
| | 5 / 6 / Unknown | 18 (4) / 30 (6) / 2 (<1) | 0 / 9 (2) / 0 |
| IFN experienced, n (%) | | 118 (24) | 100 (31) |
| IL28B CC, n (%) | | 166 (33) | 136 (31) |
| Mean HCV RNA, $\log_{10}$ IU/mL (range) | | 6.1 (2.7–7.6) | 6.2 (4.0–7.6) |

Jacobson I, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-12.

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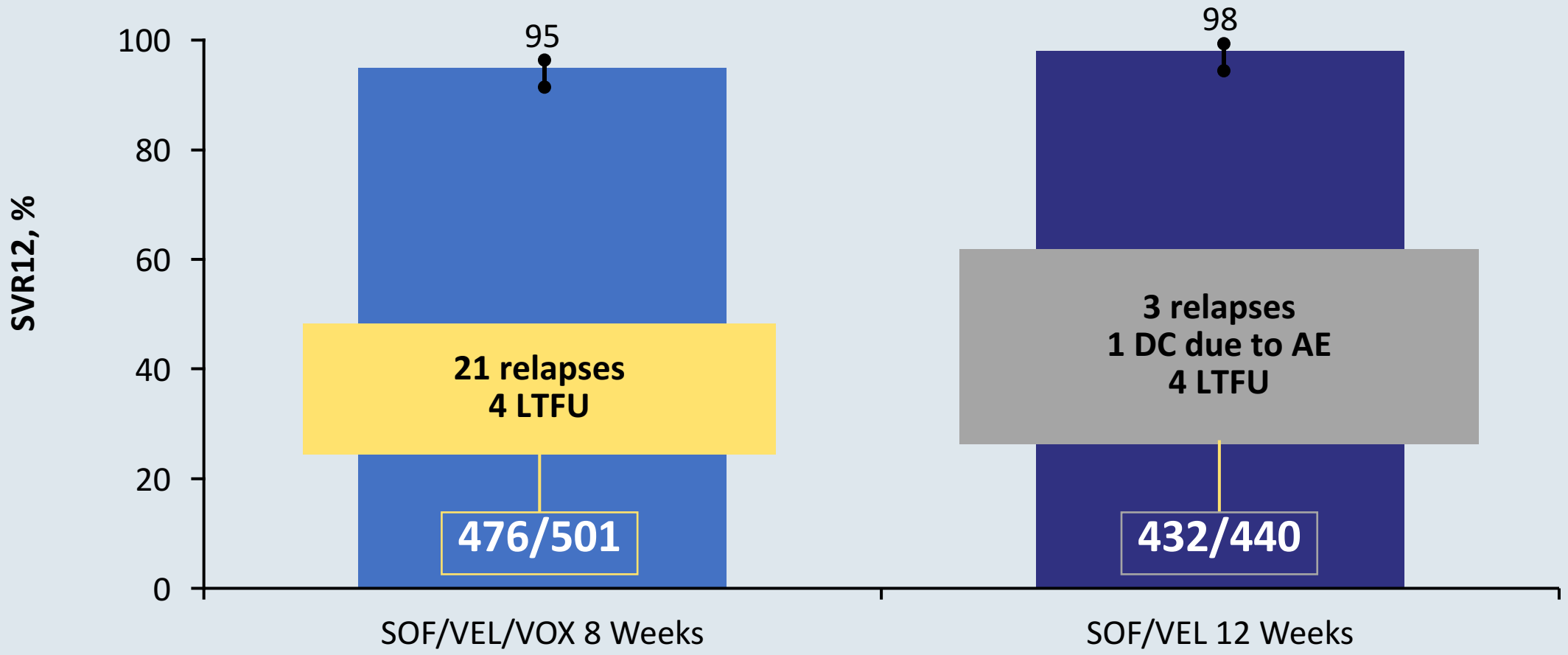
# POLARIS-2: SVR12 in GT1-6 Patients +/- Cirrhosis




Jacobson I, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-12.

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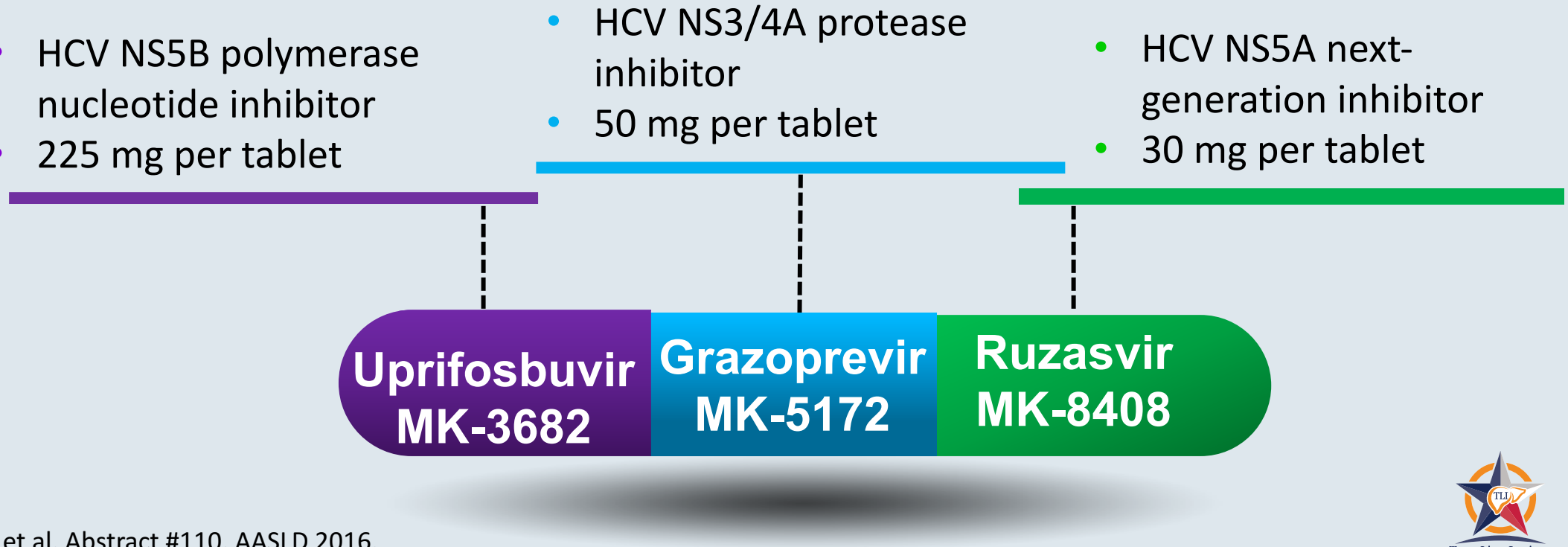
# MK3: Uprifosbuvir/Grazoprevir/Ruzasvir

- MK3 is a three-drug regimen formulated into a fixed-dose combination tablet. The regimen is given as two tablets, once-daily, without regard to food.




Lawitz E, et al. Abstract #110, AASLD 2016.

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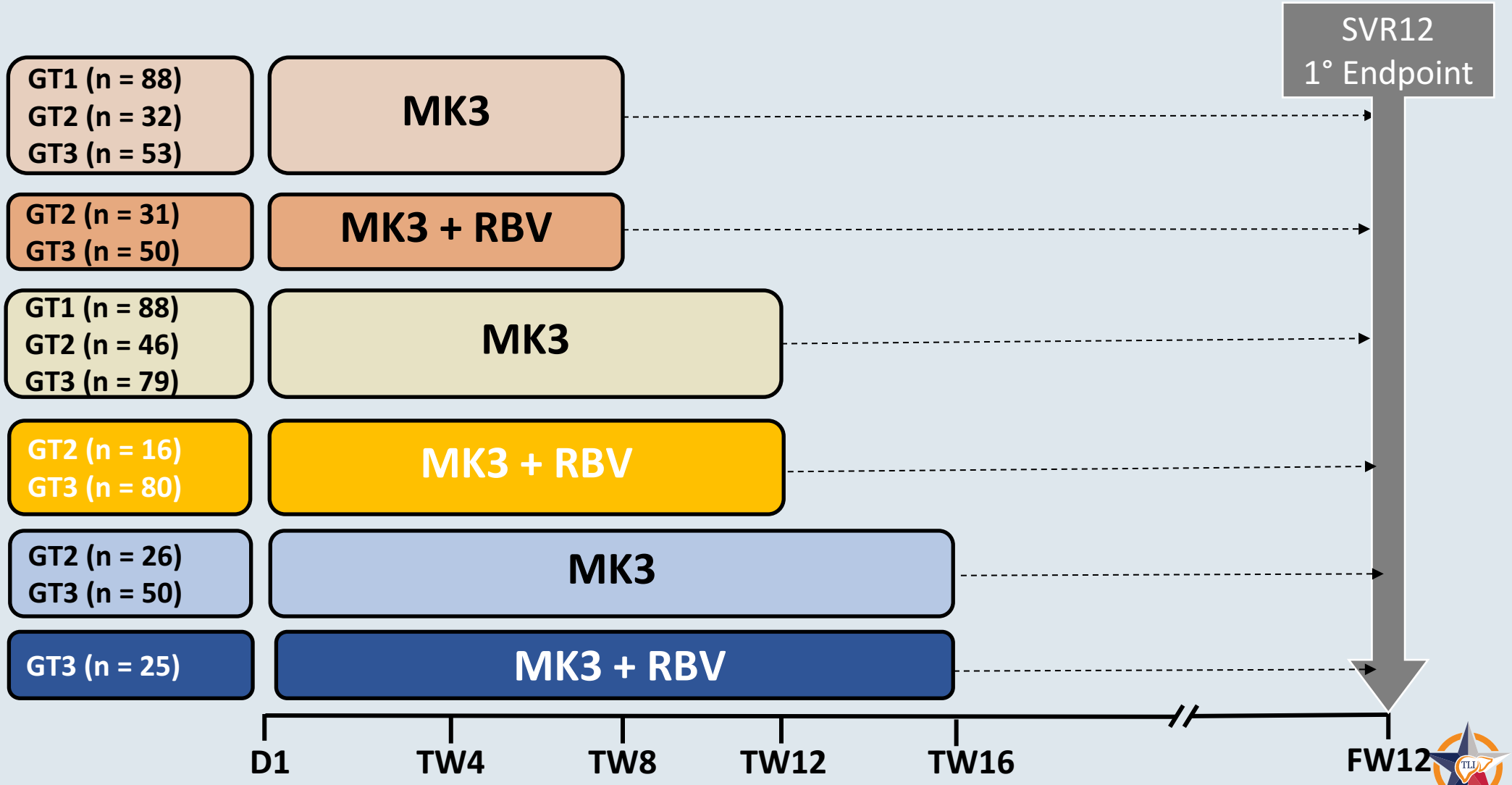
# C-CREST Design, Part B (MK3: Uprifosbuvir/Grazoprevir/Ruzasvir; N=664)




Lawitz E, et al. Abstract #110, AASLD 2016.

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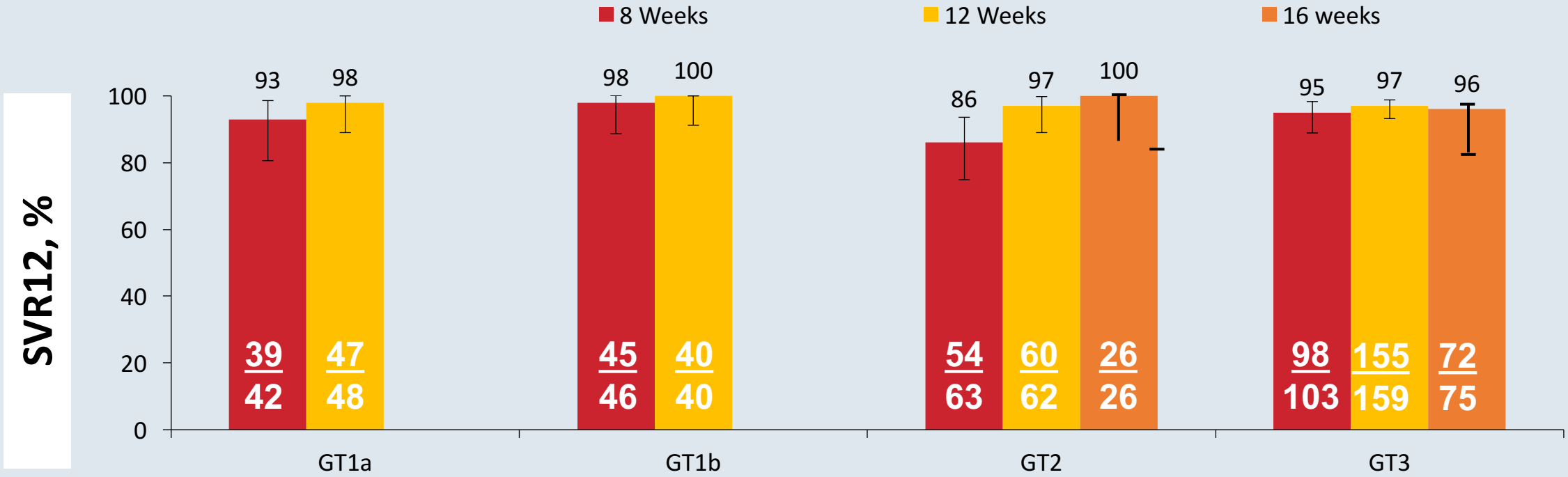
# MK3 Regimen: SVR12 by Genotype: 8, 12 or 16 Weeks




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Relapse** | **2** | **0** | | **1** | **0** | | **7** | **0** | **0** | | **4** | **3** | **2** |
| **Discontinuation (DR-AE)*** | **0** | **0** | | **0** | **0** | | **1** | **0** | **0** | | **0** | **0** | **0** |
| **Reinfection*** | **1** | **0** | | **0** | **0** | | **0** | **0** | **0** | | **0** | **0** | **0** |
| **Non-virologic failure*** | **0** | **1** | | **0** | **0** | | **1** | **2** | **0** | | **1** | **1** | **1** |

Lawitz E, et al. Abstract #110, AASLD 2016.

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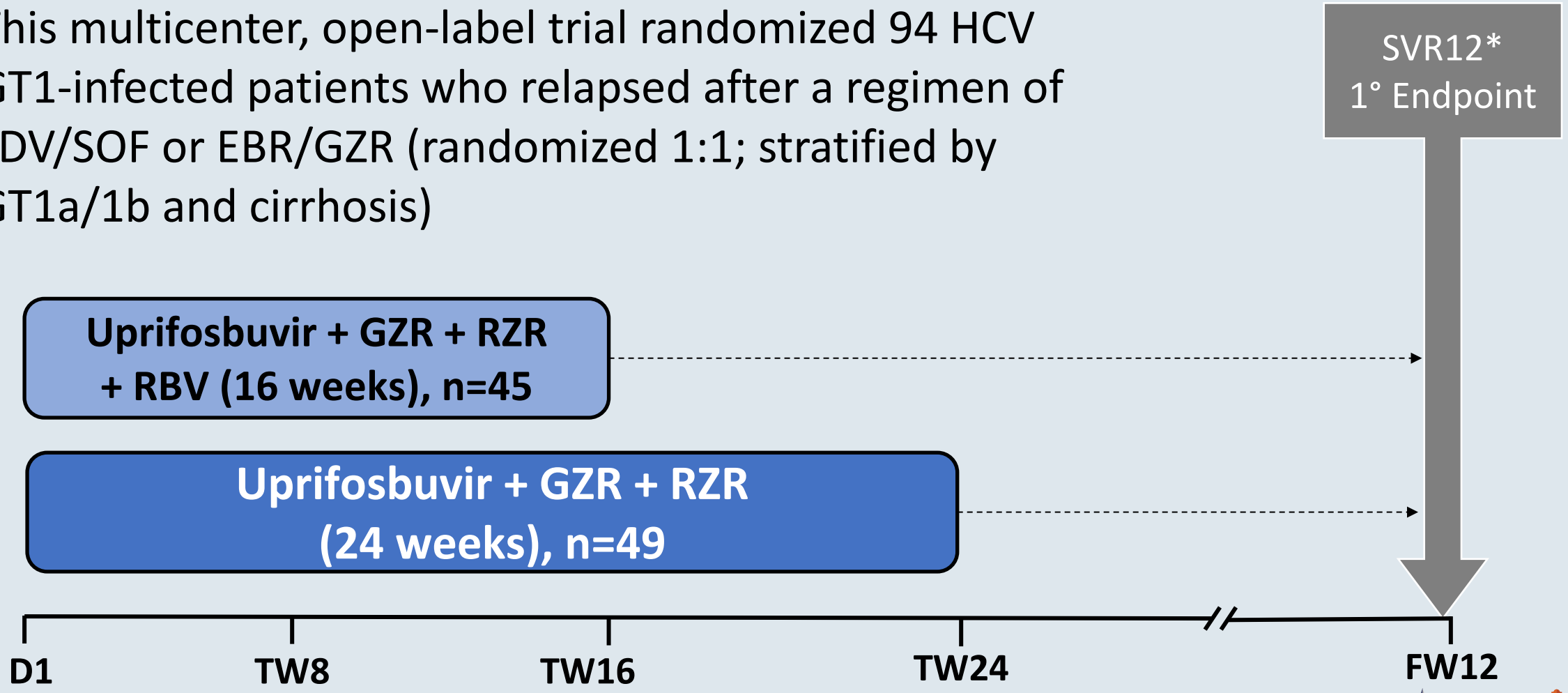
# C-SURGE: Study Design

This multicenter, open-label trial randomized 94 HCV GT1-infected patients who relapsed after a regimen of LDV/SOF or EBR/GZR (randomized 1:1; stratified by GT1a/1b and cirrhosis)




Wyles D, et al. Abstract #193, AASLD 2016.

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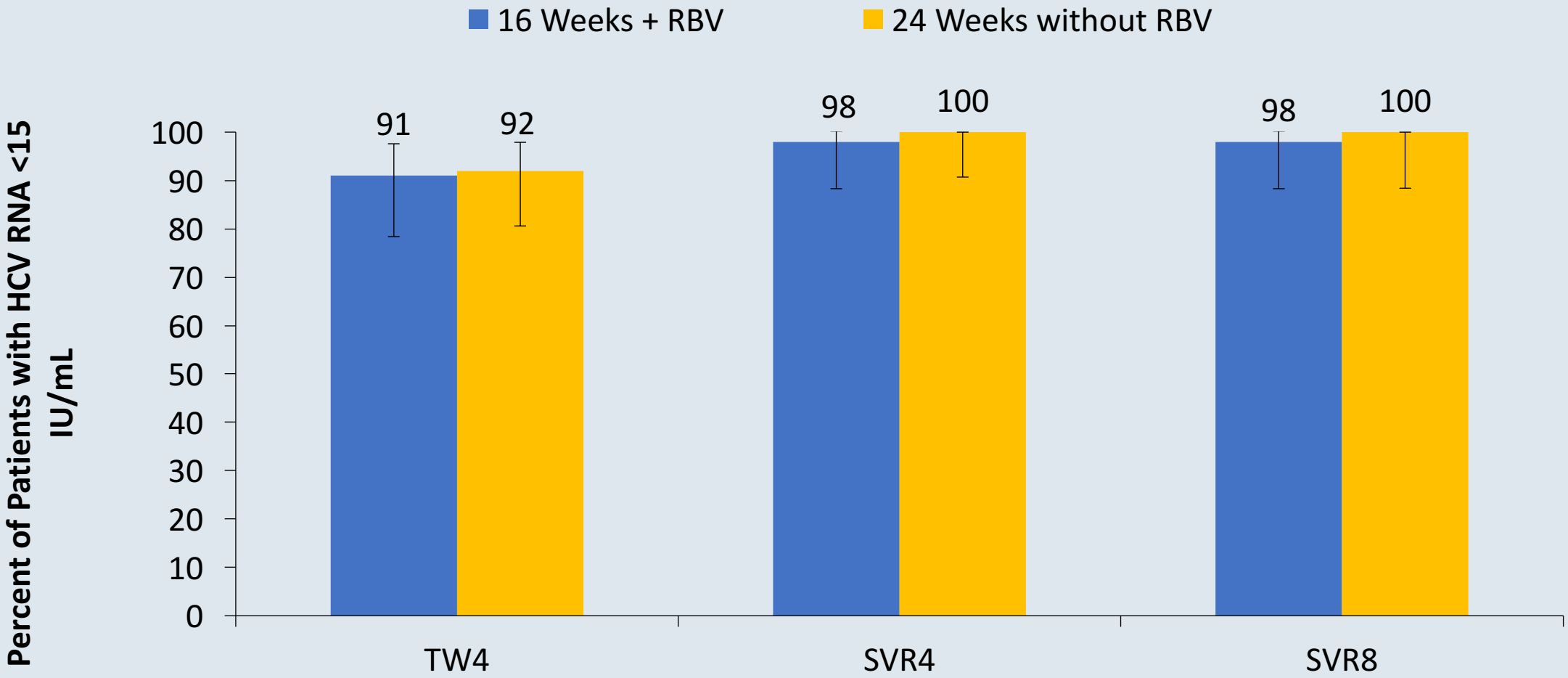
# C-SURGE: Virologic Response for M3+RBV x 16 Weeks vs M3 x 24 Weeks




Wyles D, et al. Abstract #193, AASLD 2016.

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# Summary

- Resistance associated substitutions (RASs) are common in patients not cured with DAA regimens
  - NS3 RASs are not persistent; NS5A RASs persist and represent a stable shift in the patient's HCV quasi-species
- SOF/VEL/VOX
  - Pan-genotypic and potent regimen that will be 8 weeks in duration for most patient types
  - For treatment naïve, 8 weeks of SOF/VEL/VOX no better than 12 weeks of SOF/VEL
- GLE/PIB (G/P)
  - Pan-genotypic and potent regimen that will be 8 weeks in duration for most patient types
- MK3 Regimen
  - Triple co-formulation of glazoprevir, ruzasvir, and uprifosbuvir
  - Pangenotypic and may be 8-16 weeks in various scenarios

# Roundtable Discussion/Q&A

Dr. Poordad and Angie Coste

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