# Safety and Efficacy of Sofosbuvir/Velpatasvir for the Treatment of Chronic Hepatitis C Infection in Children and Adolescents Aged 3 to 17 Years Old Through 24 Weeks Posttreatment

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## Introduction

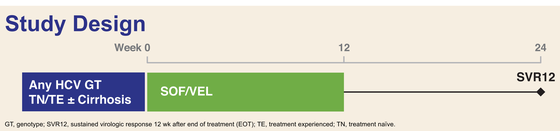
- Globally, 3.3 million adolescents and children have been estimated to have chronic hepatitis C virus (HCV) infection[1]
- Prevalence of HCV in children and adolescents in the USA is increasing in association with the opioid epidemic[2]
- Treating pediatric patients is important to achieve the WHO goal of global elimination of HCV in 2030
- The present study (NCT03022981) was conducted to evaluate the safety and efficacy of sofosbuvir (SOF)/velpatasvir (VEL) in patients aged 3–17 y with chronic HCV infection through 24 wk posttreatment

## Objectives

- Primary:
  - To assess the safety and tolerability of SOF/VEL in pediatric patients
  - To evaluate the pharmacokinetics (PK) of SOF/VEL in pediatric patients relative to adults
- Secondary: to assess the efficacy of SOF/VEL for 12 wk in pediatric patients with chronic HCV

## Methods

### Study Design




GT, genotype; SVR12, sustained virologic response 12 wk after end of treatment (EOT); TE, treatment experienced; TN, treatment naive.

- Open-label study in TN or interferon (IFN)–experienced (± ribavirin [RBV] ± a protease inhibitor) patients aged 3–<18 y with chronic HCV infection of any GT
  - 3 sequential age groups
  - Conducted at 28 sites in Belgium, Italy, UK, and USA
- PK lead-in phase in ≥17 patients in each age group to confirm the dose to be studied prior to expansion of treatment phase
- Doses and formulations of SOF/VEL:
  - 12–17 y: 400/100 mg given as 1 x 400/100-mg tablet or 2 x 200/50-mg tablets
  - 6–11 y: 200/50 mg given as 1 x 200/50-mg tablet or 4 x 50/12.5-mg oral granules packets
  - 3–5 y: ≥17 kg—200/50 mg given as 4 x 50/12.5-mg oral granules packets; <17 kg—150/37.5 mg given as 3 x 50/12.5-mg oral granules packets

### Assessments

- Efficacy was assessed by HCV RNA at each visit analyzed by COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 (Roche Molecular Diagnostics, Pleasanton, CA)
  - Key efficacy endpoint: SVR12 (HCV RNA < lower limit of quantitation [<15 IU/mL] at posttreatment Week [PTW] 12)
  - Maintenance of SVR assessed at PTW 24 (SVR24)
  - Nonstructural protein 5A (NS5A) and 5B (NS5B) resistance-associated substitutions (RASs) were identified using deep sequencing, with a 15% cutoff at baseline for patients with a virologic outcome and at virologic failure
- Safety:
  - Adverse events (AEs) and laboratory tests through PTW 4
  - Weight, height, and body mass index (BMI) through PTW 24, and radiographic bone age via wrist X-ray at baseline and PTW 24
    - Weight, height, and BMI percentile scores were calculated using 2000 Centers for Disease Control and Prevention reference charts[3]
  - Tanner stages of development for pubic hair (girls and boys), breasts (girls), and genitalia (boys)[4,5] were assessed at each visit unless stage 5 had been reached at preceding visit
- PK:
  - Steady-state exposures of SOF, its primary metabolite GS-331007, and VEL were determined on Day 7 in the PK lead-in phase in each age group
  - Population-PK modeling and simulations were conducted using intensive and sparse PK sampling data from all study patients to compare exposures with adults, and to develop a weight-based dosing regimen

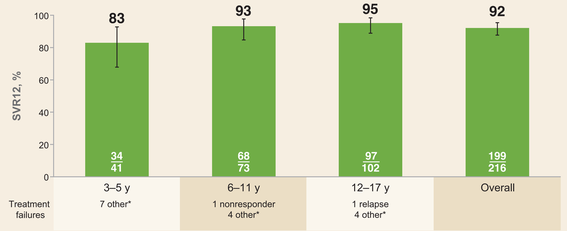
## Results

### Demographics and Baseline Characteristics

| | 3–5 y n=41 | 6–11 y n=73 | 12–17 y n=102 |
|---|---|---|---|
| Median age, y (range) | 4 (3–5) | 8 (6–11) | 15 (12–17) |
| Female, n (%) | 24 (59) | 38 (52) | 52 (51) |
| White, n (%) | 32 (78) | 66 (90) | 74 (73) |
| Mean weight, kg (range) | 19 (13–35) | 30 (18–78) | 61 (22–147) |
| Mean height, cm (range) | 106 (86–126) | 129 (107–159) | 162 (129–188) |
| Mean BMI, kg/m$^2$ (range) | 17.0 (13.9–22.0) | 17.5 (12.8–30.9) | 22.7 (12.9–48.9) |
| HCV GT, n (%) | | | |
| 1 | 32 (78) | 56 (77) | 77 (75) |
| 2 | 6 (15) | 2 (3) | 5 (5) |
| 3 | 2 (5) | 11 (15) | 12 (12) |
| 4 | 1 (2) | 4 (5) | 2 (2) |
| 6 | 0 | 0 | 6 (6) |
| Baseline HCV RNA ≥800,00 IU/mL, n (%) | 20 (49) | 35 (48) | 59 (58) |
| TE, n (%)* | 0 | 4 (5) | 22 (22) |
| Cirrhosis, n (%) | 0 | 0 | 0 |
| Vertical transmission (infected mother), n (%) | 40 (98) | 69 (95) | 91 (89) |

*Pegylated (PEG)–IFN (n=3), PEG-IFN+RBV (n=22), or PEG-IFN+RBV+telaprevir (n=1).

### SVR12: SOF/VEL for 12 Weeks in Pediatric Patients




*"Other" failures were nonvirologic failures due to early treatment discontinuation and/or loss to follow-up.

- Overall virologic failure rate: 1% (2/216)
  - TN girl aged 10 y with HCV GT 1a had a nonresponse after 8 wk of treatment and discontinued SOF/VEL
  - TN girl aged 17 y with HCV GT 1a became pregnant, discontinued treatment at Week 4, and relapsed at PTW 4
  - No children aged 3–5 y had virologic failure
- All patients who achieved SVR12 also achieved SVR24

### Virologic Resistance

#### Prevalence of Baseline RASs

| n/N(%)* | Baseline NS5A RAS | Baseline NS5B RAS |
|---|---|---|
| 3–5 y | 6/33 (18) | 1/30 (3) |
| 6–11 y | 7/68 (10) | 0/66 (0) |
| 12–17 y | 16/98 (16) | 5/97 (5) |

*N=patients with baseline deep-sequencing results.

- All patients with baseline RASs achieved SVR12

#### Virologic Resistance at Virologic Failure

- Patient aged 10 y with nonresponse at Week 8 had NS5A RAS L31V emerge
- Patient aged 17 y who relapsed did not have any RASs emerge

### Overall Safety

| | | 3–5 y n=41 | 6–11 y n=73 | 12–17 y n=102 |
|---|---|---|---|---|
| Overall Safety | Any AE | 32 (78) | 59 (81) | 77 (75) |
| | Grade 3–4 AE | 0 | 1 (1) | 2 (2) |
| | Serious AE | 0 | 2 (3) | 2 (2) |
| | Treatment discontinuation due to AE | 1 (2) | 2 (3) | 0 |
| Laboratory Abnormalities | Grades 3–4 | 1 (2) | 0 | 5 (5) |

- A girl aged 6 y had a Grade 3 serious AE of auditory hallucinations assessed by the investigator as treatment related, which resulted in treatment discontinuation
  - 3 patients had serious AEs considered unrelated to treatment, which resolved without treatment interruption
- 2 additional patients had AEs that were considered treatment related and led to treatment discontinuation: a girl aged 8 y had a Grade 1 AE of spitting up study drug, and a boy aged 3 y had Grade 1 AEs of decreased appetite, increased hyperactivity, and spitting up study drug, and a Grade 2 AE of irritability

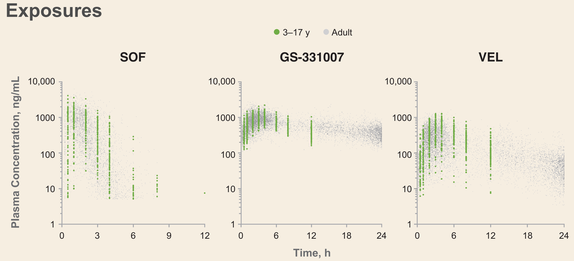
### Adverse Events in >10% of Patients in ≥1 Age Group

| Patients, n (%) | 3–5 y n=41 | 6–11 y n=73 | 12–17 y n=102 |
|---|---|---|---|
| Headache | 2 (5) | 11 (15) | 30 (29) |
| Vomiting | 11 (27) | 12 (16) | 9 (9) |
| Fatigue | 5 (12) | 9 (12) | 22 (22) |
| Nausea | 0 | 5 (7) | 17 (17) |
| Cough | 6 (15) | 11 (15) | 10 (10) |
| Pyrexia | 6 (15) | 8 (11) | 10 (10) |
| Rhinorrhea | 6 (15) | 4 (5) | 4 (4) |
| Nasal congestion | 5 (12) | 4 (5) | 6 (6) |
| Diarrhea | 5 (12) | 6 (8) | 7 (7) |
| Abdominal pain | 2 (5) | 9 (12) | 6 (6) |

- AE profile was consistent with that in adults in the Phase 3 SOF/VEL clinical trials

### Pharmacokinetics

#### Exposures




#### Weight-Based Dosing

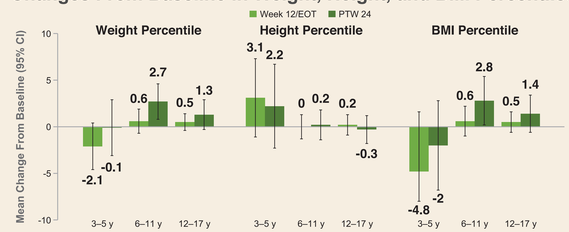
| Body Weight | SOF/VEL FDC Daily Dose |
|---|---|
| ≥30 kg | 400/100 mg |
| 17–<30 kg | 200/50 mg |
| <17 kg | 150/37.5 mg |

FDC, fixed-dose combination.

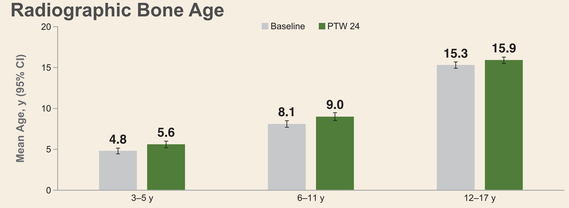
- SOF/VEL doses used in the study resulted in exposures in patients aged 3–17 y comparable to those observed in adults
- Population PK simulations using SOF, GS-331007, and VEL data from clinical studies in pediatric and adult patients support weight-based dosing for pediatric patients aged ≥3 y

### Growth and Development

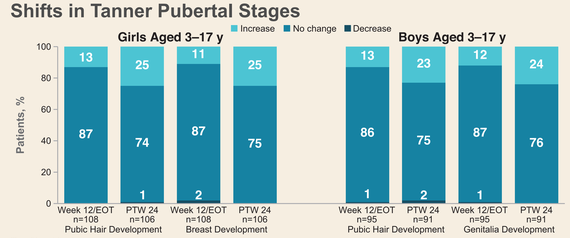
#### Changes From Baseline in Weight, Height, and BMI Percentiles




#### Radiographic Bone Age




#### Shifts in Tanner Pubertal Stages




CI, confidence interval.

- No effects on growth or development were observed in girls or boys aged 3–17 y

## Conclusions

- SOF/VEL for 12 wk resulted in SVR12 rate of 92% overall in pediatric patients aged 3–17 y regardless of HCV GT, prior treatment experience, or presence of compensated cirrhosis
  - Virologic failure rate was 1%
- SOF/VEL was well tolerated
- Population-PK simulations support weight-based dosing in this population
- Low-dose FDC tablets and granule formulations of SOF/VEL have been developed for children aged <12 y
- SOF/VEL for 12 wk currently is approved in the USA for patients with chronic HCV infection aged ≥6 y or weighing ≥17 kg
  - Regulatory submissions for children aged 3–5 y are pending

**References:** **1.** Schmelzer J, et al. Lancet Gastroenterol Hepatol 2020;5:374-92; **2.** Koneru A, et al. MMWR Morb Mortal Wkly Rep 2016;65:705-10; **3.** US Dept of Health & Human Services. CDC Growth Charts; 12/7/16; **4.** Marshall WA, Turner JM. Arch Dis Childhood 1969;44:291-303; **5.** Marshall WA, Turner JM. Arch Dis Childhood 1970;45:13-23.

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