

# Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Adolescents With Chronic Hepatitis C Virus: Part 1 of the DORA Study

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The pangenotypic regimen of glecaprevir and pibrentasvir (G/P) is approved to treat adults with chronic hepatitis C virus (HCV) infection and has yielded high cure rates in adults in clinical trials. Approved treatment options for pediatrics may include ribavirin. A pangenotypic regimen for pediatric patients remains an unmet need. DORA is an ongoing phase 2/3, nonrandomized, open-label study evaluating the pharmacokinetics (PK), safety, and efficacy of G/P in pediatric patients with chronic HCV. This analysis includes Part 1 of the study, conducted in adolescent patients 12-17 years of age given the adult regimen of G/P (300 mg/120 mg) once daily for 8-16 weeks according to the indication durations used in adults. Patients were either treatment naïve or experienced with interferon-based regimens. The primary PK endpoint was steady-state exposures for glecaprevir and pibrentasvir; the primary efficacy endpoint was sustained virologic response 12 weeks after treatment (SVR12). The secondary efficacy endpoints were on-treatment virologic failure, relapse, and reinfection. Safety and tolerability were monitored. Part 1 enrolled 48 adolescent patients infected with genotypes 1, 2, 3, or 4, of whom 47 were administered G/P. All 47 patients (100%) achieved SVR12. No on-treatment virologic failures or relapses occurred. PK exposures of glecaprevir and pibrentasvir were comparable to exposures in adults. No adverse events (AEs) led to treatment discontinuation, and no serious AEs occurred. **Conclusion:** Adolescent patients with chronic HCV infection treated with G/P achieved a comparable exposure to adults, 100% SVR12 rate, and safety profile consistent with that in adults. This pangenotypic regimen demonstrated 100% efficacy within the adolescent population in as little as 8 weeks of treatment. (HEPATOLOGY 2019;0:1-7).

Approximately 13.2 million children between the ages of 1 and 15 years are chronically infected with hepatitis C virus (HCV) globally.<sup>(1)</sup> Although the symptoms of chronic HCV infection in the pediatric population are usually mild, the consequences of disease progression in children and adolescents are similar to those in adults, especially in the context of comorbidities such as

*Abbreviations: AE, adverse event; AUC, area under the plasma concentration-time curve; BMI, body mass index; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; LDV, ledipasvir; PedsQL, Pediatric Quality of Life Inventory; PK, pharmacokinetics; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; SVR12, sustained virologic response 12 weeks after dosing.*

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obesity, alcohol use, and viral coinfections (human immunodeficiency virus [HIV], hepatitis B virus [HBV]), which can accelerate the development of severe liver disease.<sup>(1)</sup> Psychosocial health and cognitive functioning of children with chronic HCV have been shown to be impaired compared with children without HCV, and improvement in quality of life has been reported in adolescents achieving sustained virologic response (SVR).<sup>(1)</sup> The goals and endpoint of therapy are therefore the same regardless of age: cure of infection and prevention of progression of HCV infection, such as HCV-related liver disease. In addition, early treatment in children can reduce the risk of transmission, as children can be treated before they reach the age when transmission risks occur.<sup>(1)</sup>

HCV treatment options for the pediatric population are limited; sofosbuvir (SOF) plus ledipasvir

(LDV) and SOF plus ribavirin (RBV) are approved, interferon (IFN)-free, direct-acting antiviral (DAA) treatments for children aged >12 years,<sup>(2,3)</sup> with treatment durations of 12–24 weeks. A pangenotypic, RBV-free regimen with shorter durations for pediatric patients remains an unmet need.

The HCV NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir are DAAs coformulated to make up a once-daily, fixed-dose, oral combination therapy (G/P) approved in adults with chronic HCV infection.<sup>(4)</sup> Treatment with G/P in clinical trials yielded  $\geq 95\%$  sustained virologic response at posttreatment week 12 (SVR12) rates across all HCV genotypes; virologic failure rates were 0%–1%,<sup>(5–9)</sup> with an 8-week treatment duration recommended for all treatment-naïve patients without cirrhosis regardless of genotype or other baseline characteristics. The G/P regimen has been approved to treat several

following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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HCV-infected adult patient subpopulations, including those with prior DAA treatment experience, compensated cirrhosis, severe renal impairment, or HIV-1 coinfection as well as those who have had liver and kidney transplants. G/P has also been approved for use in adolescents by the European Medicines Agency at the time of manuscript drafting.

The DORA study evaluated the pharmacokinetics (PK), safety, and efficacy of G/P in pediatric patients with chronic HCV infection. This analysis includes Part 1 of the study, conducted in adolescent patients 12-17 years of age who received the adult regimen of G/P, using the same treatment durations as indicated for adults; Part 2 is ongoing in children aged 3-11 years and evaluates a pediatric formulation of G/P at age-appropriate doses.

## Patients and Methods

DORA (NCT03067129) is an ongoing phase 2/3, nonrandomized, open-label, multicenter study. The trial protocol was approved by the independent ethics committee or institutional review board for each trial center. The trial was conducted in accordance with the Good Clinical Practice Guidelines and the ethical principles of the Declaration of Helsinki; all parents/guardians provided written informed consent, and patients provided assent where required.

Patients  $\geq 12$  to  $< 18$  years of age with chronic HCV genotype (GT) 1-6 infection (HCV RNA  $\geq 1,000$  IU/mL) were eligible to enroll. Patients with decompensated cirrhosis (Child-Pugh B/C) or HBV coinfection were excluded. Notably, infection with multiple or mixed HCV genotypes, presence of compensated cirrhosis, and coinfection with HIV (on stable antiretroviral therapy appropriate for G/P coadministration) were eligible to enroll. An assessment of liver fibrosis was mandatory before enrollment. Patients with no history of cirrhosis who did not have a liver biopsy within 24 months or FibroScan within 6 months before screening had a FibroTest performed at screening to determine presence or absence of cirrhosis.

G/P (300 mg/120 mg) was dosed orally with food once daily, and treatment durations were assigned according to genotype, presence or absence of cirrhosis, and prior HCV treatment status (Supporting Tables S1 and S2).

The primary PK endpoint was the steady-state area under the plasma concentration-time curve (AUC) values at 0 to 24 hours for glecaprevir and pibrentasvir. Exposures of glecaprevir and pibrentasvir were characterized using population pharmacokinetic approach with data from all the enrolled 47 adolescents. Intrinsic factors (e.g., demographics) that accounted for the variability in glecaprevir and pibrentasvir pharmacokinetics were determined and quantified using a stepwise forward inclusion, backward elimination model building procedure. The final models were evaluated based on goodness-of-fit plots, visual predictive checks, and nonparametric bootstrap. The nonlinear mixed-effects modeling software NONMEM was used for all data analysis and simulation-based model evaluations.

The primary efficacy endpoint was the proportion of patients with SVR12 (HCV RNA less than 15 IU/mL at posttreatment week 12), assessed in the intention-to-treat (ITT) population, which included all patients who received at least one dose of study drug. The secondary endpoints were  $C_{max}$  and clearance of glecaprevir and pibrentasvir as well as the proportion of patients with on-treatment virologic failure, post-treatment relapse, and reinfection. Polymorphisms in HCV NS3 and NS5A were identified by next-generation sequencing from patient samples collected at baseline.

Safety and tolerability were evaluated by monitoring adverse events (AEs), postbaseline laboratory test values, physical examination findings, vital signs, and growth and development. AEs were recorded using the Medical Dictionary for Regulatory Activities Preferred Terms. Severity, seriousness, and relationship to treatment were assessed by trial investigators. Worsening from baseline during treatment in laboratory test values was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events.

Demographics, efficacy, and safety analyses were performed on the ITT population. Efficacy endpoints were summarized with a two-sided 95% confidence interval (CI), using the normal approximation to the binomial distribution. The Wilson's score method was used to calculate the CI when the number of SVR12 nonresponders was less than 5.

Quality of life was evaluated by the Pediatric Quality of Life Inventory (PedsQL) scale, a patient-reported outcomes instrument validated in studies of

**TABLE 1. Baseline Demographics and Clinical Characteristics**

Characteristic	Total (n = 47)
Sex	
Female	26 (55)
Male	21 (45)
Race	
White	35 (75)
Black	4 (9)
Asian	6 (13)
Multiple	2 (4)
HCV genotype*	
1a/1b subtype	24 (51)/13 (28)
2	3 (6)
3	4 (9)
4	3 (6)
Age (years)	14 (12-17)
Weight (kg)	58 (32-109)
Cirrhosis status	
No cirrhosis	47 (100)
Prior HCV treatment history	
Naïve	36 (77)
Experienced	11 (23)
Type of previous regimen	
IFN-based	11 (23)
HCV RNA (log <sub>10</sub> IU/mL)	6.2 (4.6-7.2)
Baseline HCV RNA level (IU/mL)	
<1,000,000	21 (45)
≥1,000,000 and <2,000,000	4 (9)
≥2,000,000	22 (47)
Baseline fibrosis stage	
F0-F1	45 (96)
F2	1 (2)
F3	1 (2)
Treatment-experienced	11 (23) <sup>†</sup>
HCV/HIV-coinfected	2 (4)
Yes	2 (4)
No	45 (96)
Baseline polymorphisms, n/N <sup>‡</sup>	
NS3 only	0
NS5A only	11/44 (25)
NS3 + NS5A	0
None	33/44 (75)

Note: Data are presented as n (%) or median (range).

\*No patients with HCV GT 5 or GT 6 were enrolled, although they were eligible per protocol.

<sup>†</sup>All experienced with pegylated IFN and RBV; no SOF-experienced patients were enrolled.

<sup>‡</sup>Baseline polymorphisms detected by next-generation sequencing using 15% detection threshold at amino acid positions: NS3: 155, 156, 168; NS5A: 24, 28, 30, 31, 58, 92, 93. n = number of patients with baseline polymorphisms in the respective target(s); N = number of patients with available sequences in both targets.

**TABLE 2. Steady-State Pharmacokinetics Parameters of Glecaprevir and Pibrentasvir in HCV-Infected Adolescent and Adult Patients**

Population	G/P 300 mg/120 mg qd Adult Formulation*	
	Glecaprevir AUC <sub>24</sub> (ng•hour/mL)	Pibrentasvir AUC <sub>24</sub> (ng•hour/mL)
HCV-infected adolescents (12 to <18 years of age, n = 47)	4,380 (157) [2,688-70,300]	1,440 (47) [428-3,380]
HCV-infected adults without cirrhosis	4,800 (122) [123-297,000]	1,430 (57) [148-14,200]

\*Geometric mean (CV%) [minimum-maximum].

Abbreviations: AUC<sub>24</sub>, area under the plasma concentration-time curve from time 0 to 24 hours at steady-state; CV, coefficient of variation; qd, once daily.

the pediatric population and in pediatric subjects who have chronic health conditions.<sup>(10,11)</sup> An increase from baseline in the PedsQL score indicates improvement in quality of life.

Growth and development were evaluated by growth rate and height and body mass index (BMI) z scores. Growth rate was defined as the change in height over change in age from the previous visit. Height and BMI z scores were calculated using World Health Organization published height/BMI-for-age z scores.

## Results

Part 1 of the study enrolled 48 adolescent patients; one patient was never dosed and thus was excluded from all analyses. As shown in Table 1, the majority of patients were HCV treatment naïve (77%) and with HCV GT 1 infection (79%); all were without cirrhosis, although patients with cirrhosis were allowed to enroll. Of the patients with prior treatment experience (23%), all were experienced with pegylated IFN and RBV. The majority of patients (85%, 40/47) had acquired HCV perinatally. Most patients received 8 weeks of therapy (94%, 44/47), and 3 patients received 16 weeks of therapy (6%, 3/47; GT 3, treatment experienced). Based on the characteristics of patients who enrolled in the study, no patients were assigned to 12 weeks of therapy. Two patients coinfecting with HIV were enrolled.

Glecaprevir and pibrentasvir mean steady-state exposures (AUC) in the HCV-infected adolescent patients were 4,380 ng•hour/mL and 1,440 ng•hour/mL,

respectively, and were comparable to the reported mean glecaprevir and pibrentasvir AUC values of 4,800 ng•hour/mL and 1,430 ng•hour/mL, respectively, in HCV-infected adults without cirrhosis (Table 2).<sup>(4)</sup> No clinically meaningful relationship between weight and exposures or between age and exposures was observed in the adolescent patients.

The overall SVR12 rate was 100% (47/47; 95% CI, 92.4-100.0). No patients discontinued treatment, and there were no virologic failures. The presence of baseline polymorphisms in NS3 or NS5A (Table 1) had no impact on SVR12. Both patients with HIV-1 coinfection maintained HIV-1 viral suppression.

The safety and tolerability profile of G/P was noted to be consistent with the safety profile of G/P established for adults in clinical trials (Table 3). The majority of AEs were mild and unrelated to G/P. There were no serious AEs and no AEs leading to discontinuation of study drug. The most common AEs (occurring in ≥10% of patients) were nasopharyngitis, upper respiratory tract infection, headache, fatigue, oropharyngeal pain, and pyrexia; there were no grade 3 or higher aminotransferase or bilirubin elevations, no liver-related toxicities, and no cases of drug-induced liver injury (DILI; Table 3). Treatment does not appear to have an impact on growth and development, with a mean change from baseline to posttreatment week 12 of ±0.1 for the BMI and height z scores, respectively.

Among 44 patients with available data, improvements in patient-reported quality of life total PedsQL

score, physical health summary score, and psychosocial health summary score were observed. At the final treatment visit, the mean change from baseline in psychosocial score was 2.4 (SD = 9.2) and the mean change from baseline in physical score was 2.0 (SD = 9.2), for an overall improvement in total score of 2.3 (SD = 7.7).

## Discussion

Although the G/P regimen has been demonstrated to be safe and effective in specific HCV-infected patient subpopulations including those with DAA experience, compensated cirrhosis, severe renal impairment, HIV-1 coinfection, and liver and kidney transplants, it does not include a wide indication for patients <18 years of age, and pangenotypic ribavirin-free regimens remain an unmet need for the pediatric population. Here, we report evidence of a short-duration pangenotypic regimen for children <18 years.

In this study, 100% of adolescents treated with G/P achieved SVR12, with the majority of patients taking the 8-week treatment duration. The steady-state exposures of glecaprevir and pibrentasvir in HCV-infected adolescents were within the range of those observed in HCV-infected adults, and the safety profile of G/P in adolescents was consistent with that in adults. The majority of the most common AEs were unrelated to G/P as assessed by the clinical investigators. In particular, the most common AEs reported (e.g., nasopharyngitis and upper respiratory infection) are most likely consistent with seasonal variations of illnesses common in the adolescent population and are therefore unrelated to G/P. The majority of adolescents were enrolled in the study over the 2017-2018 cold and flu season, which was notable for increased reported rates and severity of flu-like illnesses.<sup>(12,13)</sup> Fatigue was reported as the most common AE related to G/P, which is consistent with the AE profile established in adults. No serious AEs or AEs resulting in treatment discontinuation were reported. No hepatic laboratory abnormalities indicative of DILI occurred. Decline in quality of life was not observed.

Adults with HCV infection have several approved IFN- and RBV-free DAA treatment options; in contrast, children with HCV infection have limited options, with further restrictions based on HCV genotype and age. Previously, pegylated IFN alfa and

**TABLE 3. Summary of Safety and Tolerability**

Adverse event, n (%)	Total, n = 47
Any AE	41 (87)
Serious AE	0
AE leading to drug discontinuation	0
AEs in ≥10% of all patients	
Nasopharyngitis	12 (26)
Upper respiratory tract infection	9 (19)
Headache	8 (17)
Fatigue	5 (11)
Oropharyngeal pain	5 (11)
Pyrexia	5 (11)
Laboratory abnormalities	
ALT, grade ≥3 (>5 × ULN)	0
AST, grade ≥3 (>5 × ULN)	0
Total bilirubin, grade ≥3 (>3 × ULN)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

ribavirin treatment has shown encouraging results in children and adolescents with chronic HCV infection, but with lower SVR rates as compared with DAAs, and long treatment durations up to 48 weeks.<sup>(14,15)</sup> There are currently two approved regimens in the United States and Europe for adolescents with HCV infection. SOF/LDV is approved for adolescents with HCV GT 1, 4, 5, or 6 infection; sofosbuvir plus ribavirin is approved for adolescents with HCV GT 2 or 3 infection. Treatment with 12-week SOF/LDV regimen resulted in 98% SVR12 in 98/100 patients with HCV GT 1 or 4 infection, with 2 patients lost to follow-up.<sup>(16)</sup> SOF plus RBV was dosed for 12 weeks or 24 weeks in patients with HCV GT 2 or 3 infection, respectively. Treatment resulted in 97% SVR12 in 38/39 patients with GT 3 infection (1 lost to follow-up) and 100% SVR12 in 13 patients with HCV GT 2 infection.<sup>(17)</sup> In this latter study, the AE profile of adolescents was consistent with a ribavirin-containing regimen. In the DORA study, the G/P regimen was used to treat patients with HCV GT 1, 2, 3, or 4 infection (GT 5 and 6 patients were allowed but did not enroll), and all patients treated achieved SVR12; notably, there were no discontinuations, either due to adverse events or lost to follow-up, and the majority of subjects received the 8-week treatment duration (94%). In Europe, G/P has been approved for use in adolescents 12 years of age and older.

Although eligibility criteria allowed for enrollment of patients with compensated cirrhosis and patients with prior SOF experience, no patients meeting these criteria were enrolled. Therefore, the efficacy and safety of G/P in these adolescent subgroups could not be directly assessed. However, given the similarity of HCV infection in children and adults, and in particular, the comparable PK exposures, high SVR12 rates, and favorable safety profile similar to those observed in adults from these subgroups treated with G/P in clinical trials, efficacy and safety in subgroups not enrolled may be extrapolated based on the data established within the adult G/P trials. Similarly, although enrollment was open to all major genotypes, including mixed and indeterminate genotypes, there were no GT 5 or 6 patients enrolled. All patients enrolled in the DORA study achieved SVR12, regardless of GT, including those with HCV GT 2, 3, and 4 infection. As with the other subgroups not represented in the study, efficacy and safety for GT 5- and GT 6-infected patients may be extrapolated from the adult data,

given no GT-dependent PK difference and comparable PK between adolescent and adult patients.

Although HCV infection in children is largely physically asymptomatic and mild, cure of infection should be pursued to positively impact the quality of life in these children in addition to achieving global HCV elimination. Perinatal transmission and high-risk practices such as intravenous drug abuse and intrafamilial transmission are significantly contributing to increased rates of HCV infections.<sup>(18)</sup> Treatment of HCV infection in the adolescent population will decrease the pool of HCV-infected young adults. Therefore, treatment and management of chronic HCV infection in the adolescent population will not only mitigate the development of progressive liver injury but also prevent further transmission of HCV. To achieve this goal, a short-duration pangenotypic IFN- and RBV-free treatment option, with improved tolerability and high SVR rates, could provide assurance that early treatment is a viable option, rather than deferring treatment until adulthood. This study is a registrational trial that reported using a pangenotypic regimen in the adolescent population. These results demonstrate that G/P has a favorable safety profile among adolescents consistent with the favorable safety profile observed in adults. G/P is a short-duration pangenotypic regimen efficacious in adolescents with chronic HCV infection regardless of GT, a population with limited RBV-free treatment options.

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