DR. STEVEN LOBRITTO (Orcid ID : 0000-0003-1482-1128)

PROF. ETIENNE SOKAL (Orcid ID : 0000-0001-5597-4708)

Article type : Rapid Communication

Title Page:

Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in children with chronic hepatitis C virus: part 2 of the DORA study

Authors: Maureen M Jonas[1], Susan Rhee[2], Deirdre A Kelly[3], Antonio Del Valle-Segarra[4], Cornelia Feiterna-Sperling[5], Susan Gilmour[6], Regino P Gonzalez-Peralta[7], Loreto Hierro[8], Daniel H Leung[9], Simon C Ling[10], Yuri Lobzin[11], Steven Lobritto[12], Tatsuki Mizuochi[13], Michael R Narkewicz[14], Vishakha Sabharwal[15], Jessica Wen[16], Hoi Kei Lon[2], John Marcinak[2], Andrew Topp[2], Rakesh Tripathi[2], Etienne Sokal[17]

Affiliations: [1]Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, United States; [2]AbbVie Inc., North Chicago, Illinois, United States; [3]The Liver Unit, Birmingham Women's & Children's Hospital and University of Birmingham, Birmingham, United Kingdom; [4]San Jorge Children's Hospital, San Juan, Puerto Rico; [5]Department of Pediatric Pulmonology, Immunology, and Intensive Care Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany; [6] Stollery Children's Hospital, and University of Alberta, Alberta, Canada; [7]AdventHealth for Children and AdventHealth Transplant

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/HEP.31841

Institute, Orlando, Florida, United States; [8]Hospital Universitario La Paz, Madrid, Spain; [9]Division of Gastroenterology, Hepatology, and Nutrition, Texas Children's Hospital and Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States; [10]Division of Gastroenterology, Hepatology, and Nutrition, The Hospital for Sick Children, and Department of Paediatrics, University of Toronto, Toronto, Canada; [11] Pediatric Research and Clinical Center for Infectious Diseases, Russian Federation; North-Western State Medical University named after I.I. Mechnikov, Russian Federation; St Petersburg, Russia; [12]Morgan Stanley Children's Hospital of NY, Columbia University Irving Medical Center, New York, New York, United States; [13]Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume, Japan; [14]Digestive Health Institute, Children's Hospital Colorado, Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics University of Colorado School of Medicine, Aurora Colorado, United States; [15]Division of Pediatrics Infectious Diseases, Department of Pediatrics, Boston University Medical Center, Boston, Massachusetts, United States; [16]The Children's Hospital Philadelphia and University of Pennsylvania, Philadelphia, Pennsylvania, United States; [17]Université Catholique de Louvain, Cliniques Universitaires Saint Luc, Division of Pediatric Gastroenterology and Hepatology, Brussels, Belgium

Keywords: direct-acting antiviral, pediatric, pangenotypic, chronic HCV

Email addresses of all authors: Jonas MM, Maureen.Jonas@childrens.harvard.edu; Rhee S, susan.rhee@abbvie.com; Kelly DA, deirdrekelly@nhs.net; Del Valle-Segarra A, adelvalle1126@live.com; Feiterna-Sperling C, cornelia.feiterna-sperling@charite.de; Gilmour S, susan.gilmour@albertahealthservices.ca; Gonzalez-Peralta RP, Regino.Gonzalez-Peralta.md@adventhealth.com; Hierro L, marial.hierro@salud.madrid.org; Leung DH, dhleung@texaschildrens.org; Ling SC, simon.ling@sickkids.ca; Lobzin Y, ylobzin@mail.ru; Lobritto S, sjl12@cumc.columbia.edu; Mizuochi T, mizuochi_tatsuki@kurume-u.ac.jp; Narkewicz MR, Michael.Narkewicz@childrenscolorado.org; Sabharwal V, vishakha.sabharwal@bmc.org; Wen J, wenj@email.chop.edu; Lon HK, hoikei.lon@abbvie.com; Marcinak J, john.marcinak@abbvie.com;

Topp A, andrew.topp@abbvie.com; Tripathi R, rakesh.l.tripathi@AbbVie.com; Sokal E, etienne.sokal@uclouvain.be

Footnote Page:

Corresponding Author:

Maureen M. Jonas, M.D.

Center for Childhood Liver Disease, Boston Children's Hospital

300 Longwood Avenue

Boston, MA 02115

Email: Maureen.jonas@childrens.harvard.edu

Tel: 617-355-5837

Abbreviations: HCV, hepatitis C; HCC, hepatocellular carcinoma; ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology, and Nutrition; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; AASLD, American Association for the Study of Liver Diseases; DAA, direct-acting antiviral; SVR12, sustained virologic response at post-treatment week 12; LDV/SOF, ledipasvir/sofosbuvir; SOF, sofosbuvir; RBV, ribavirin; SOF/VEL, sofosbuvir/velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; pegIFN, pegylated interferon; PK, pharmacokinetics; HBV, hepatitis B virus; IPK, intense pharmacokinetics; AUC, area under the plasma concentration time curve; ITT, intention-to-treat; CI, confidence interval; Cmax, maximum concentration; AE, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; PTW, post-treatment week

Word Count: 3553

Funding: The design, study conduct, analysis, and financial support of the study (NCT03067129) was provided by AbbVie. AbbVie sponsored the study, and participated in the study design, research,

analysis, data collection, interpretation of data, review, and approval of the content. All authors had access to all relevant data and participated in writing, review, and approval of this manuscript. No honoraria or payments were made for authorship.

Ethics and consent statement: The trials were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved at all sites by their independent ethics committees or institutional review boards prior to enrollment.

Data Availability: AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

COI:

AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the abstract. All authors had access to relevant data, and participated in the writing, review, and approval of the abstract. No honoraria or payments were made for authorship.

Maureen M. Jonas: Consultant (DSMB) and grant support from Gilead; grant support from AbbVie, Echosens, Merck, and Roche **Deirdre A. Kelly:** Grant/research support: AbbVie, Gilead Sciences, Roche; Consultant/advisor: Roche **Antonio Del Valle-Segarra:** Investigator in an AbbVie-sponsored clinical study **Cornelia Feiterna-Sperling:** Investigator in sponsored studies: AbbVie, Gilead **Susan Gilmour:** Investigator in an AbbVie-sponsored clinical study **Regino P. Gonzalez-Peralta:** Grant support from Gilead, AbbVie, and Merck; advisory committee with Gilead, Alexion, Albireo **Loreto Hierro:** Investigator in AbbVie-sponsored clinical study **Daniel H. Leung:** Grant support from AbbVie, Gilead, and Mirum; medical advisory committee for Merck and Gilead **Simon C. Ling:** Grant support

from AbbVie and Gilead **Yuri Lobzin:** Nothing to disclose **Steven Lobritto:** Grant support from AbbVie; advisory committee with Kadmon and Gilead **Tatsuki Mizuochi:** Investigator in an AbbVie-sponsored clinical study **Michael R Narkewicz:** Consultant for Vertex; grant support from AbbVie and Gilead **Vishakha Sabharwal:** Investigator in an AbbVie-sponsored clinical study **Jessica Wen:** Consultant and grant support from Gilead; grant support from AbbVie and Alexion **Etienne Sokal:** Founder, Chairman of the Board of directors and member of the executive committee, Promethera Biosciences **Susan Rhee, Hoi Kei Lon, John Marcinak, Andrew Topp, Rakesh Tripathi:** Employee of AbbVie Inc. and may hold stock or options

Abstract:

Background and Aims: Glecaprevir/pibrentasvir (GLE/PIB) has shown high efficacy and safety in chronic hepatitis C virus (HCV)-infected adults and adolescents; data in children were limited. DORA

part 2 is a phase 2/3, nonrandomized, open-label study evaluating the pharmacokinetics, efficacy, and safety of a pediatric formulation of glecaprevir (GLE) and pibrentasvir (PIB) in children ages 3 - < 12 years old. *Approach and Results:* Children with chronic HCV infection, genotype (GT) 1-6, with or without compensated cirrhosis, were divided into 3 cohorts by age, cohort 2 (9 – < 12 years), cohort 3 (6 – < 9 years), and cohort 4 (3 – < 6 years) and given weight-based doses of GLE and PIB for 8, 12, or 16 weeks. Primary endpoints were SVR12 and steady-state exposure; secondary endpoints were rates of persistent viremia, relapse, and reinfection. Safety and laboratory abnormalities were assessed. Final pediatric dosages determined to be efficacious were 250 mg GLE + 100 mg PIB (in children weighing ≥ 30 kg to < 45 kg), 200 mg GLE + 80 mg PIB (≥ 20 kg to < 30 kg), and 150 mg GLE + 60 mg PIB (12 kg to < 20 kg). Of 80 participants enrolled and dosed, 96% (77/80) achieved SVR12. One participant, on the initial dose ratio, relapsed by post-treatment week 4; no participants had virologic failures on the final dose ratio of GLE 50 mg/PIB 20 mg. Two non-responders prematurely discontinued the study. Most adverse events (AEs) were mild; no drug-related serious AEs occurred. Pharmacokinetic exposures were comparable to adults. *Conclusions:* A pediatric formulation of GLE/PIB was highly efficacious and well-tolerated in chronic HCV-infected children 3 - < 12 years old.

Globally, 71 million people are infected with hepatitis C virus (HCV); of those, approximately 13.2 million are children between 1 and 15 years of age.(1, 2) Vertical transmission is the primary route of viral acquisition in pediatrics.(2) While 20% of children infected this way may clear HCV infection spontaneously in the first few years of life, 80% will go on to develop long-term infection. HCV infection acquired during infancy or childhood can lead to chronic hepatitis and cirrhosis; hepatocellular carcinoma (HCC) has also been reported in children.(2-4) Guidance from the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the American Association for the Study of Liver Diseases (AASLD) recommends that all children and adolescents aged ≥ 3 years with HCV infection will benefit from treatment with an approved direct-

acting antiviral (DAA) regimen, regardless of disease severity.(2, 5, 6) The goals of HCV treatment in pediatric patients are cure of infection and prevention of progression of liver disease.(2, 6)

Direct-acting antiviral therapy has demonstrated high sustained virologic response at post-treatment week 12 (SVR12) in adolescents (12 to < 18 years of age); however, options in children remains limited. While combinations of ledipasvir/sofosbuvir (LDV/SOF) and sofosbuvir (SOF) + ribavirin (RBV) have been approved in adolescents and children ≥ 3 years of age, neither combination is pangenotypic.(6-12) Currently, sofosbuvir/velpatasvir (SOF/VEL) is the only pangenotypic, RBV-free, DAA regimen approved for HCV-infected children ages 6 and older; pangenotypic options in children ≥ 3 years of age remain an unmet need.(13, 14)

A combination of glecaprevir (GLE) 100 mg and pibrentasvir (PIB) 40 mg, co-formulated as glecaprevir/pibrentasvir (GLE/PIB) into a fixed-dose tablet, has been approved in adults and adolescents > 12 years (or ≥ 45 kg) as a pangenotypic treatment option for chronic HCV infection.(15, 16) Efficacy of GLE/PIB has been demonstrated in treatment-naïve adult patients with chronic HCV infection with SVR12 rates of 96%-99.7%; it is approved for durations as short as 8 weeks in all major genotypes in both cirrhotic and non-cirrhotic treatment-naïve patients and in non-cirrhotic genotype (GT) 1, 2, 4-6 infected patients who are treatment-experienced with pegylated interferon (pegIFN), RBV, and/or SOF.(15-20) Part 1 of the DORA study evaluated the efficacy and safety of the co-formulated GLE/PIB tablet in adolescents between the ages of 12 to < 18 years for 8, 12, or 16 weeks depending on treatment experience and geographic location.(21) Of 47 chronic HCV GT1-4 infected adolescents receiving GLE/PIB, 100% achieved SVR12 with a safety and tolerability profile comparable to adults. Part 2 of the DORA study aimed to study the pharmacokinetics (PK), efficacy and safety of a pediatric formulation of GLE/PIB in chronic HCV-infected children with GT1-6, utilizing the same treatment durations used in adults and adolescents.

METHODS:

DORA (NCT03067129) is a phase 2/3, non-randomized, open-label, multinational study; part 2 of the study evaluated children 3 - < 12 years of age (cohorts 2-4), who were given a pediatric formulation

of GLE/PIB from 2 May 2018 - 28 May 2020. 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 study participants provided assent where required.

Participants were eligible to enroll if they were 3 - < 12 years old at the time of enrollment and had chronic HCV GT1 – 6 infection. Participants could be without cirrhosis or with compensated cirrhosis, treatment-naïve, or treatment-experienced with an interferon-based regimen (± RBV) or SOF with RBV (± pegIFN) and with or without HIV-1 co-infection. Participants were required to have an HCV RNA ≥ 1000 IU/mL at the time of screening; fibrosis was determined by biopsy, FibroScan or FibroTest. Participants without a history of cirrhosis that had not had a liver biopsy within 24 months or a FibroScan within 6 months prior to screening underwent a FibroTest to determine presence or absence of cirrhosis. Study participants were excluded if they were co-infected with hepatitis B virus (HBV), had decompensated cirrhosis (Child-Pugh B/C or a Child-Pugh Score ≥ 7) or if they had HCC. Participants were divided into 3 age cohorts: 9 - < 12 years (cohort 2), 6 - < 9 years (cohort 3) and 3 - < 6 years (cohort 4) (Figure 1). Study participants were dosed by weight within the age cohorts. In each cohort, participants were first enrolled in parallel into an intense pharmacokinetics (IPK) portion to characterize the PK and safety in each age group, followed by a non-IPK safety/efficacy portion. Study participants enrolled in the IPK portion had to be HIV-negative, treatment-naïve, and with an identified HCV GT. Participants were treated with a pediatric formulation of GLE/PIB, comprised of small film-coated granules of GLE and PIB, for 8 or 12 weeks depending on the presence of cirrhosis and geographical location, as prescribed durations for adults and adolescents vary by region. For the IPK arm, the initial dose of GLE/PIB was administered to a subset of participants, based on the child's weight and age at screening. IPK participants underwent an intensive PK sampling scheme at Week 2 with blood samples taken at hours 0, 2, 4, 6 and 12 post-dose. After the initial subset of participants completed the IPK visit, PK samples were analyzed to determine if any dose adjustments were needed. The IPK results from the initial subset of

participants were evaluated to determine if therapeutic efficacious exposures were attained, comparable to adults. Enrollment into the non-IPK safety and efficacy portions began when the dosing recommendations per age group based on the PK and clinical data from the IPK analysis were ascertained. Children in the non-IPK efficacy/safety arm of the study were administered GLE/PIB for 8, 12, or 16 weeks based on HCV GT, cirrhosis status, prior treatment experience and geographical location. The non-IPK portion of the study received a formulation of GLE/PIB identical to the IPK portion; however, the granules were packaged in unit dose sachets for daily oral administration. All participants and their caregivers received a Study Drug Dosing Card containing dosing instructions for administration of GLE/PIB; the dosing instructions given to participants and their caregivers specified the pediatric formulation was to be administered by mixing the granules with a small amount (1-2 teaspoons) of a soft food vehicle, such as hazelnut spread, Greek yogurt or peanut butter.

The primary PK endpoint was steady state area under the plasma concentration-time curve (AUC) values at 0 and 24 hours for GLE and PIB.

Demographics, efficacy, and safety analyses were performed on the intention-to-treat (ITT) population, which included all enrolled participants who received at least 1 dose of the study drug. The primary efficacy endpoint was the percentage of participants with SVR12 (HCV RNA < 15 IU/mL). Plasma HCV RNA levels were collected using the COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test v2.0 (Roche Diagnostics); HCV RNA samples were collected at screening, Day 1, Weeks 2, 4, 8, 12 (for those on 12- and 16 weeks of GLE/PIB therapy) and at the time of treatment completion or if a participant prematurely discontinued therapy. The efficacy endpoint was calculated with a 2-sided 95% confidence interval (CI) using the normal approximation to the binomial distribution. If the number of participants who failed to achieve SVR12 was < 5, the Wilson's score method was used to determine the CI instead.

The secondary endpoints were maximum concentration (Cmax), apparent clearance of GLE and PIB, the percentage of participants with persistent viremia (defined as 2 consecutive HCV RNA

measurements of > 1 $\log_{10}$ IU/mL above nadir at any time during treatment or confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < 15 IU/mL), post-treatment HCV relapse, and HCV re-infection rates. To assess palatability and tolerability, parents completed a Palatability Questionnaire to provide feedback on the perception of the GLE/PIB granule dosage form. The Palatability Questionnaire included 5 questions related to the administration and ingestion of GLE/PIB formulation.

Safety and tolerability were evaluated by monitoring adverse events (AEs), post baseline laboratory values, physical examination findings, vital signs, growth and development. Adverse events were tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term overall and by age group. Laboratory samples were collected at baseline, at treatment Weeks 2, 4, 8, 12 and 16, and at post-treatment week (PTW) 4 – 144; trial investigators assessed the severity and relationship to treatment. Laboratory values that worsened from baseline during treatment were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events - v4.0.

Baseline polymorphisms were determined based on the availability of samples. For all participants who experienced virologic failure and had an HCV RNA ≥ 1000 IU/mL, post-baseline substitutions relative to the baseline sequence and to the appropriate prototypic reference sequence were tabulated and summarized.

RESULTS:

Eighty-one HCV-infected children, ages 3 to < 12 years, were enrolled; 80 children were dosed and divided into 3 cohorts based on age; one participant in cohort 4 was enrolled but not dosed. The majority of participants were treatment-naïve (78/80, 98%) and infected with HCV GT1 (58/80, 73%) (Table 1); the two treatment-experienced study participants had been treated with pegIFN and RBV. Eleven participants had FibroScan scores prior to Study Day 1 and 77 participants had baseline FibroTest scores; although allowed by inclusion criteria, none of the enrolled study participants had cirrhosis. Seventy-eight participants received DAA therapy for 8 weeks. One GT3-infected participant in Japan received therapy for 12 weeks and one GT3, treatment-experienced participant received

therapy for 16 weeks, both in accordance with the local adult prescribing label duration. One participant who was co-infected with HIV received 8 weeks of treatment.

Following the IPK analysis from the first 17 enrolled participants that received the initial GLE/PIB dose ratio of 40 mg/15 mg, the dose was adjusted to the final GLE/PIB dose ratio of 50 mg/20 mg. The final doses of GLE 250 mg + PIB 100 mg (in children weighing ≥ 30 kg - < 45 kg), GLE 200 mg + PIB 80 mg (in children weighing ≥ 20 kg - < 30 kg), or GLE 150 mg + PIB 60 mg (in children weighing 12 kg - < 20 kg) were used in the remaining IPK participants and in the non-IPK group. The geometric mean steady-state exposures of the final doses of GLE and PIB were 4600 ng·hour/mL and 1720 ng·hour/mL, respectively for participants weighing ≥ 30 kg to < 45 kg, 6020 ng·hour/mL and 1700 ng·hour/mL, respectively for participants weighing ≥ 20 kg to < 30 kg, and 6340 ng·hour/mL and 1410 ng·hour/mL for participants weighing 12 kg to < 20 kg, compared to 4800 ng·hour/mL and 1430 ng·hour/mL, respectively for adults (Table 2). Figure 2 shows the distribution of AUC in adults and adolescents (who received the adult GLE/PIB formulation at the 300 mg/120 mg dose), as well as in children across the 3 cohorts who received the pediatric formulation of GLE/PIB at the final doses.

The overall SVR12 rate was 96% (77/80, 95% CI, 90%, 99%); the SVR12 rates were 93% (27/29, 95% CI, 78%, 98%) for cohort 2 (9 - <12 years old), 100% (27/27, 95% CI, 88%, 100%) for cohort 3 (6 - < 9 years old) and 96% (23/24, 95% CI, 80%, 99%) for cohort 4 (3 - < 6 years old), respectively (Figure 3).

No participants experienced virologic failure on the final GLE/PIB dose ratio of 50 mg/20 mg and no new HCV infections or reinfections were reported. One 9-year-old treatment-naïve participant with HCV GT3b infection who received the initial dose ratio of GLE/PIB 40 mg/15 mg for 8 weeks relapsed by PTW4. This child had no baseline polymorphism or treatment-emergent substitutions in NS3 but had K30R and V31M in NS5A at baseline and had treatment-emergent substitution Y93H in NS5A. There were two premature discontinuations; one 3-year-old child refused to swallow the GLE/PIB granule formulation; the participant was partially dosed on Day 1 without subsequent doses, and thus included in the ITT population analysis. Another 11-year-old participant discontinued treatment by Day 4 due to a drug-related rash.

Adverse events occurred in 71% of children, with 29% being deemed reasonably related to GLE/PIB by the study investigators (Table 3). The most common AEs (occurring in ≥ 10% of participants) were headache (14%), vomiting (14%), and diarrhea (10%). One child experienced a non-serious, grade 3 drug-related AE of erythematous rash and discontinued GLE/PIB by Day 4 and another child experienced an unrelated AE of respiratory tract infection, which led to a brief interruption of GLE/PIB. This participant resumed GLE/PIB to completion and achieved SVR12. No participants experienced clinically significant laboratory abnormalities and there were no cases of liver-related toxicities. No treatment-emergent serious AEs were reported. One serious AE of osteomyelitis (considered unrelated to GLE/PIB) was reported in the post-treatment period on Day 171.

Seventy-seven study participants or their caregivers completed the Palatability Questionnaire at Week 2, 68 participants or their caregivers completed the questionnaire at Week 8 and 78 participants or their caregivers completed the questionnaire at the final treatment visit. At the final treatment visit, 32% of participants/caregivers rated the formulation/dosing very convenient and an additional 40% of participants/caregivers rated the formulation/dosing as convenient. 82% of participants disliked the taste of the medicine and 53% reported disliking the texture. Most study participants/caregivers reported taking the dose within 5 minutes or less (85%).

DISCUSSION:

Several DAA regimens are licensed to treat adults with chronic HCV infection but therapeutic options for children are limited. Interferon and RBV-based therapies are less effective and more toxic than DAA regimens and few studies have evaluated DAA therapy in children younger than 12 years old.(6) In one study, HCV-infected children ages 6-11 years old who received 12 weeks of SOF/LDV achieved an SVR12 rate of 99% (91/92); in another study, children 3 – ≤ 6 years of age who received 12 weeks of SOF/LDV achieved an SVR12 rate of 97% (33/34).(11, 12)

GLE/PIB treatment was associated with a SVR12 in 100% in part 1 of the DORA study evaluating 48 adolescents, 47 of whom received the adult formulation; the other participant was not dosed.(21) Subsequently, the AASLD guidance included the recommendation for a fixed-dose regimen of

GLE/PIB 300mg/120 mg for 8-16 weeks in HCV-infected GT1 – 6 adolescents, aged ≥ 12 years or weighing ≥ 45 kg.(6) For children ≥ 3 years of age with HCV GT 1,4,5 or 6, weight based LDV/SOF is recommended for 12 weeks.

In part 2 of the DORA study, 80 pediatric study participants, 3 - < 12 years of age, received a pediatric formulation of GLE/PIB, based on age and weight; the majority (98%) were treated for 8-weeks. Seventy-seven participants achieved SVR12 (96%). Of the 3 who did not achieve SVR12, one HCV GT3b-infected participant relapsed by PTW4, one discontinued GLE/PIB due to an AE of a rash and one participant was enrolled but received only one dose of GLE/PIB. As only one child relapsed on the initial dose ratio, negative baseline predictors/trends such as demographics, baseline HCV RNA level, genotype, or presence of baseline polymorphisms were not identified. Adverse events were mostly mild in severity, and similar to the safety profile established in adults and adolescents; no treatment-emergent serious AEs and no liver-related toxicities were reported. The taste of GLE/PIB was disliked by 82% of participants at the final treatment visit; in comparative HCV medication therapies for children, 5 participants reported disliking the taste of LDV/SOF; however, only 17 children in that study were assessed for palatability.(11) Despite disliking the taste or texture of GLE/PIB, most participants were able to take the medication in 5 minutes or less, including in the younger 3 - < 6 year-old age cohort, and high SVR12 rates were similar to those seen in adults and adolescents treated with GLE/PIB.

The noncompartmental PK analysis was based on 38 participants with IPK samples, who received the final GLE/PIB daily dose ratio of 50mg/20mg. Overall, the distribution of the AUC of GLE and PIB, in HCV-infected children at each 12 kg- < 20 kg, ≥ 20 kg- < 30 kg, and ≥ 30 kg - < 45 kg weight group, as well as adolescents, were within the efficacious and safe exposure ranges of those in HCV-infected non-cirrhotic adults.

Although participation allowed for enrollment, there were no GT5 or 6-infected children enrolled and a small number of children with GT2 and GT4; the study recruited participants from North America, Japan and Europe and given the prevalence of GT and region, the lower number of

participants of GT2 and GT4 is understandable. Given PK exposure profiles similar to adults and adolescents, it may stand to reason that data may be extrapolated from these populations to children with similar GTs.

A weight-based pediatric formulation of GLE/PIB in HCV-infected children, 3 to < 12 years old, had a PK, efficacy and safety profile similar to that observed in adults and adolescents.(21) The PK results, combined with the efficacy and safety profile, support the use of using the weight-based pediatric GLE/PIB dose ratio of 50 mg/20 mg in HCV-infected children aged 3 to < 12 years of age.

Overall, the data from DORA Part 2 demonstrate that GLE/PIB is a highly efficacious and safe pangenotypic treatment option for young children with chronic HCV infection. The pediatric formulation was well tolerated, and provides a short, 8-week treatment option for children with HCV.

Acknowledgments:

The authors would like to express their gratitude to the subjects who participated in this study, and their families, as well as the study investigators and coordinators of the study. Glecaprevir was identified by AbbVie and Enanta. Medical writing support was provided by Sneh Mody, PharmD, MBA, BCCCP of AbbVie, and funded by AbbVie.

References:

1. Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161-176.
2. Indolfi G, Hierro L, Dezsofi A, Jahnel J, Debray D, Hadzic N, Czubkowski P, et al. Treatment of Chronic Hepatitis C Virus Infection in Children: A Position Paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;66:505-515.
3. Indolfi G, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C, Bulterys M, et al. Hepatitis C virus infection in children and adolescents. Lancet Gastroenterol Hepatol 2019;4:477-487.

4. Bortolotti F, Verucchi G, Camma C, Cabibbo G, Zancan L, Indolfi G, Giacchino R, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. Gastroenterology 2008;134:1900-1907.

5. Leung DH, Squires JE, Jhaveri R, Kerkar N, Lin CH, Mohan P, Murray KF, et al. Hepatitis C in 2020: A North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper. J Pediatr Gastroenterol Nutr 2020;71:407-417.

6. AASLD-IDSA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org/. Revised December 10, 2019. Accessed August 9, 2020.

7. Sovaldi (sofosbuvir) [EU Summary of Product Characteristics]. County Cork, T45 DP77, Ireland; Gilead Sciences Ireland UC, 2019.

8. Harvoni (ledipasvir and sofosbuvir) [EU Summary of Product Characteristics]. County Cork, T45 DP77; Gilead Sciences Ireland UC, 2020.

9. Harvoni (ledipasvir and sofosbuvir) [US Prescribing Information]. Foster City, CA; Gilead Sciences, Inc., 2020.

10. Sovaldi (sofosbuvir) [US Prescribing Information]. Foster City, CA; Gilead Sciences, Inc., 2020.

11. Schwarz KB, Rosenthal P, Murray KF, Honegger JR, Hardikar W, Hague R, Mittal N, et al. Ledipasvir-Sofosbuvir for 12 Weeks in Children 3 to <6 Years Old With Chronic Hepatitis C. Hepatology 2020;71:422-430.

12. Murray KF, Balistreri WF, Bansal S, Whitworth S, Evans HM, Gonzalez-Peralta RP, Wen J, et al. Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11. Hepatology 2018;68:2158-2166.

13. Jonas MM RR, Sokal EM, et al. Safety and Efficacy of sofosbuvir/velpatasvir in pediatric patients 6 to < 18 years old with chronic hepatitis C infection. *Hepatology*. 2019;70(S1):465A.

14. Epclusa (velpatasvir and sofosbuvir) [US Prescribing Information]. Foster City, CA; Gilead Sciences, Inc., 2020.

15. Mavyret (glecaprevir and pibrentasvir) [US Prescribing Information]. North Chicago, IL; AbbVie Inc., 2020.

16. Maviret EU. [Summary of Product Characteristics]. AbbVie; 2020. .

17. Wyles D, Poordad F, Wang S, Alric L, Felizarta F, Kwo PY, Maliakkal B, et al. Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: A partially randomized phase 3 clinical trial. Hepatology 2018;67:514-523.

18. Puoti M, Foster GR, Wang S, Mutimer D, Gane E, Moreno C, Chang TT, et al. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1-6 patients without cirrhosis. J Hepatol 2018;69:293-300.

19. Brown RS, Jr., Buti M, Rodrigues L, Chulanov V, Chuang WL, Aguilar H, Horvath G, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naive patients with chronic HCV genotypes 1-6 and compensated cirrhosis: The EXPEDITION-8 trial. J Hepatol 2020;72:441-449.

20. Rockstroh JK, Lacombe K, Viani RM, Orkin C, Wyles D, Luetkemeyer AF, Soto-Malave R, et al. Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients Coinfected With Hepatitis C Virus and Human Immunodeficiency Virus Type 1: The EXPEDITION-2 Study. Clin Infect Dis 2018;67:1010-1017.

21. Jonas MM, Squires RH, Rhee SM, Lin CW, Bessho K, Feiterna-Sperling C, Hierro L, et al. Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Adolescents With Chronic Hepatitis C Virus: Part 1 of the DORA Study. Hepatology 2020;71:456-462.

FIGURES/Tables:

Figure 1: Study Schematic

FIGURE 1 LEGEND: Study schematic depicting cohorts 2-4 in part 2 of the DORA study, broken down by the pharmacokinetics and efficacy/safety analyses portions, for each cohort. In the post-treatment period, participants administered at least 1 dose of the study drug will be monitored for safety, viral response, emergence and/or persistence of resistance-associated viral substitutions, growth and development.

GT, genotype; PD, pharmacodynamic; PK, pharmacokinetic

Figure 2. Distribution of AUC of GLE and PIB (at Week 2) in Adults and Adolescents Following the Adult Formulation of GLE/PIB at 300 mg/120 mg Dose and in Children Following the Pediatric Formulation of GLE/PIB at Final Determined Doses

FIGURE 2 LEGEND: Distribution of AUC of GLE and PIB (at Week 2) in Adults and Adolescents Following the Adult Formulation of GLE/PIB at 300 mg/120 mg Dose and in Pediatrics Following the Pediatric Formulation of GLE/PIB at Final Determined Doses. Dashed lines show the target GLE AUC range of (2400-9600) ng•hr/mL and target PIB AUC range of (715-2860) ng•hr/mL, which are ± 2-fold of geometric mean exposures in adults.

AUC, area under the plasma-concentration time curve; GLE, glecaprevir; PIB, pibrentasvir

Figure 3: SVR12 Rates by Cohort

FIGURE 3 LEGEND: SVR12 rates by age cohort and overall group following treatment with the weight-based GLE/ PIB pediatric formulation in the intent-to-treat population. Error bars represent 95% confidence intervals, which were calculated using the Wilson's score method.

GLE, glecaprevir; PIB, pibrentasvir; SVR12, sustained virologic response at post-treatment week 12

Table 1. Baseline Demographics and Clinical Characteristics

Baseline Characteristic	Cohort 2 9 - < 12 years old N = 29 n (%)	Cohort 3 6 – < 9 years old N = 27 n (%)	Cohort 4 3 - < 6 years old N = 24 n (%)	Cohorts 2-4 3 - < 12 years old N = 80 n (%)
Sex				
Female	15 (52)	17 (63)	12 (50)	44 (55)
Male	14 (48)	10 (37)	12 (50)	36 (45)
Race				
White	21 (72)	18 (67)	16 (67)	55 (69)
Black	1 (3)	1 (4)	1 (4)	3 (4)
Asian	5 (17)	5 (19)	4 (17)	14 (18)
Multiple	1 (3)	3 (11)	1 (4)	5 (6)
HCV genotype*				
1a/1b subtype	11 (38)/8 (28)	12 (44)/10 (37)	14 (58)/3 (13)	37 (46)/21 (26)
2	2 (7)	0	0	2 (3)
3	8 (28)	3 (11)	7 (29)	18 (23)
4	0	2 (7)	0	2 (3)
Age (years) (median, range)	10 (9 – 11)	7 (6 – 9)	4 (3-5)	7 (3 – 11)
Weight (kg) (median, range)	37 (29 – 44)	23 (20 – 34)	16 (13 – 21)	25 (13 – 44)
Prior HCV treatment history				
Naive	27 (93)	27 (100)	24 (100)	78 (98)
Treatment-experienced[†]	2 (7)	0	0	2 (3)
HCV RNA (log10 IU/mL)[§] (median, range)	6.2 (4.8 – 7.2)	5.9 (4.5 – 7.2)	5.8 (3.4 – 6.9)	6.0 (3.4 – 7.2)
Baseline HCV RNA level (IU/mL)				
<1,000,000	10 (35)	15 (56)	14 (58)	39 (49)
≥ 1,000,000 and <2,000,000	8 (28)	4 (15)	1 (4)	13 (16)
≥ 2,000,000	11 (38)	8 (30)	9 (38)	28 (35)
Baseline fibrosis stage[‡]				
F0-F1	28 (97)	26 (96)	24 (100)	78 (98)

F2	1 (3)	1 (4)	0	2 (3)
HCV/HIV-coinfected				
Yes	0	1 (4)	0	1 (1)
No	29 (100)	26 (96)	24 (100)	79 (99)
Baseline polymorphisms n/N[‖]				
NS3 only	0	0	0	0
NS5A only	4/29 (14)	10/27 (37)	4/23 (17)	18/79 (23)
NS3 + NS5A	0	0	0	0
None	25/29 (86)	17/27 (63)	19/23 (83)	61/79 (77)

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

*No participants with HCV GT5 or GT 6 were enrolled, although they were eligible per protocol

[†]Both treatment-experienced participants had received pegylated IFN and RBV

[‡] Fibrosis was determined by a liver biopsy, FibroScan®, or FibroTest

[§] HCV RNA quantified by Roche COBAS® Ampliprep/COBAS® TaqMan HCV Quantitative Test v2.0

[‖] 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 participants with baseline polymorphisms in the respective target(s); N = number of participants with available sequences in both targets.

HIV, human immunodeficiency virus; IFN, interferon; RBV, ribavirin

Table 2. Steady-State Population Pharmacokinetics of GLE and PIB Following the Final Dosing Regimen

Age Cohort and Body Weight (kg)*	GLE Dose (mg)	Geometric Mean (P5, P95) GLE AUC24ss (ng·hour/mL)	PIB Dose (mg)	Geometric Mean (P5, P95) PIB AUC24ss (ng·hour/mL)
Cohort 2 ≥ 30 to < 45 kg	250	4600 (644, 34200)	100	1720 (675, 3930)
Cohort 3 ≥ 20 to < 30 kg	200	6020 (831, 41300)	80	1700 (700, 3640)
Cohort 4 12 to < 20 kg	150	6340 (924, 43300)	60	1410 (549, 3130)

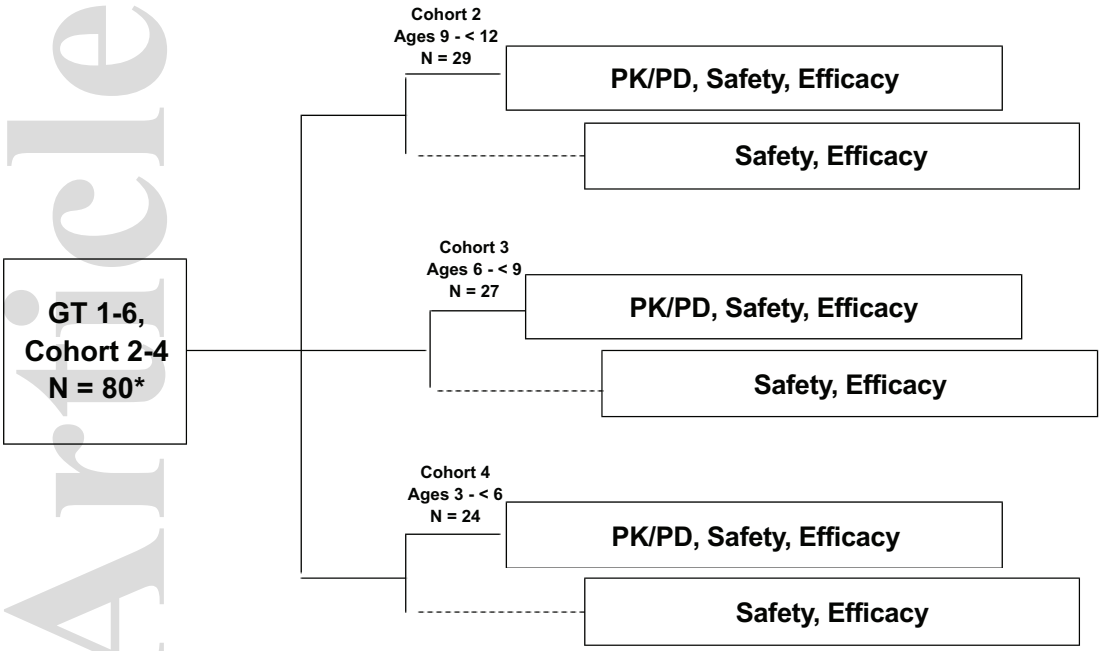
*Geometric mean is based on weight, as there were some children who fell outside the weight bands for their age cohort

AUC24ss, area under the plasma concentration-time curve from time 0 to 24 hours at steady-state; GLE, glecaprevir; P5, 5th percentile of data; P95, 95th percentile of data; PIB, pibrentasvir;

Table 3. Adverse Events and Laboratory Abnormalities

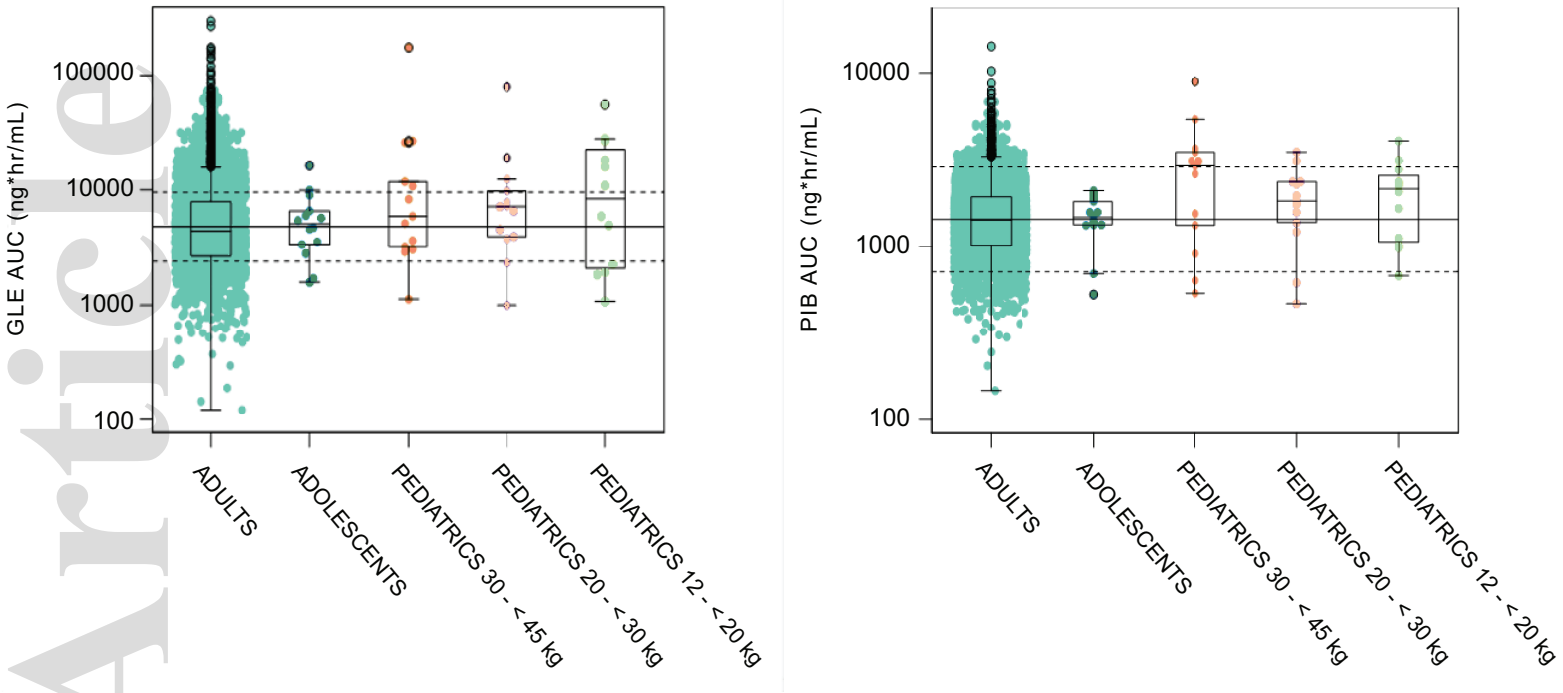
Characteristic	Overall Cohort 2-4 N = 80 n (%)
Any AE	57 (71)
Any AE with reasonable possibility of being related to GLE/PIB	23 (29)
Treatment-emergent serious AE	0
AE leading to drug discontinuation	1 (1)
AEs in ≥ 10% of all participants	
Vomiting	11 (14)
Headache	11 (14)
Diarrhea	8 (10)
Laboratory Abnormalities	
ALT, grade ≥3 (>5 x ULN)	0
AST, grade ≥3 (>5 x ULN)	0
Total bilirubin, grade ≥3 (>3 x ULN)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; GLE, glecaprevir; PIB, pibrentasvir



* Enrolled and dosed
GT, genotype; PD, pharmacodynamic; PK, pharmacokinetic

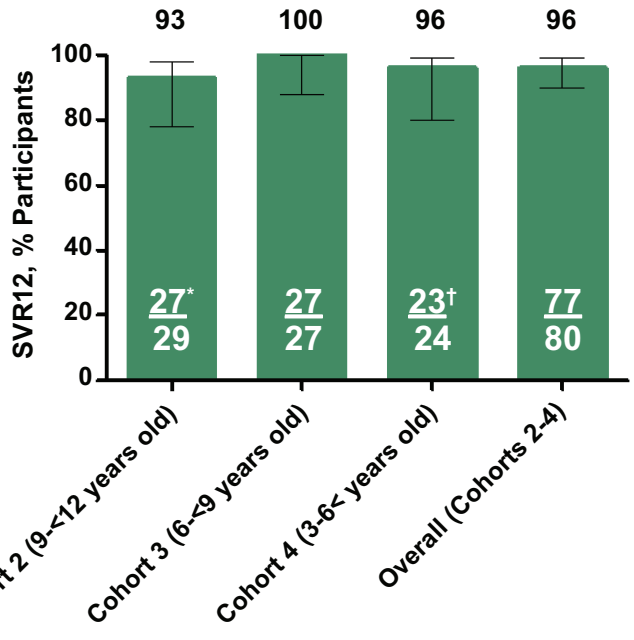
hep_31841_f1.eps



Dashed lines show the target GLE AUC range of (2400-9600) ng•hr/mL and target PIB AUC range of (715-2860) ng•hr/mL, which are ± 2-fold of geometirc mean exposures in adults.

AUC, area under the plasma-concentration time curve; GLE, glecaprevir; PIB, pibrentasvir

hep_31841_f2.eps



* One participant with premature discontinuation due to drug-related rash and one participant relapsed by PTW4

† One participant refused to swallow granule formulation and prematurely discontinued study after being partially dosed on Day 1; the participant did not receive subsequent doses

Error bars represent 95% confidence intervals. PTW, post treatment week; SVR12, sustained virologic response at Post-Treatment Week 12

hep_31841_f3.eps