Clinical and Cross-Discipline Team Leader Review

Review Completion Date	March 29, 2019
From	Nicholas Rister, MD
Through	Prabha Viswanathan, MD
Subject	Combined Clinical and Cross-Discipline Team Leader Review
NDA #	209394
Supplement#	S-006
Applicant	AbbVie Inc.
Date of Submission	October 12, 2018
Priority or Standard	Priority
PDUFA Goal Date	April 30, 2019
Proprietary Name	Mavyret®
Non-Proprietary Name	Glecaprevir (GLE)/Pibrentasvir (PIB)
Dosage form(s) / Strength(s)	GLE 100 mg/PIB 40 mg fixed dose combination tablets
Applicant Proposed Indication(s)/Population(s)	(b) (6)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult and pediatric patients 12 years of age and older or weighing at least 45 kg with HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.

1. Introduction

This combined Clinical and Cross Discipline Team Leader (CDTL) Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment of once daily glecaprevir/pibrentasvir (GLE/PIB) use in pediatric patients 12 years of age and older with chronic Hepatitis C Virus (HCV) genotype (GT) 1, 2, 3, 4, 5, and 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A).

HCV infection is a global health problem, with over 184 million individuals chronically infected worldwide. Although the prevalence of chronic HCV is lower in children than in adults, an estimated 5 million children worldwide have active HCV infection[1]. The National Health and Nutrition Examination Survey (NHANES) collected between 2003 and 2010 indicated that 0.2% of 6- to 11-year-olds (31,000 children) and 0.4% of 12- to 19-year-olds (101,000 adolescents) in the US are chronically infected with HCV[2]. There are 7 identified HCV genotypes (GT), with

GT 1 being the most prevalent worldwide. HCV GT2 and GT3 infections are more common in Latin America (5%-30%), Europe (20%-40%), and Asia (30%-45%). HCV GT4 is found in parts of Africa and the Middle East and GT6 is primarily found in southeast Asia. GT7 has recently been described in central Africa.

The goal of treatment for HCV-infected patients is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR). Historically, the first effective treatment for chronic HCV included a combination of interferons (a group of naturally occurring proteins that form an essential part of the immune system) and ribavirin (a synthetic antiviral nucleoside analogue) but these regimens were complicated by relatively low SVR rates and a multitude of side effects. An improved understanding of the HCV genome has enabled efforts to improve efficacy and tolerability of HCV treatment in recent years. This has led to the development of multiple direct-acting antivirals (DAAs), which are medications targeted at specific steps within the HCV life cycle. The current classes of DAAs include:

- NS3/4A protease inhibitors that inhibit the NS3/4A serine protease, an enzyme involved in post-translational processing and replication of HCV (**glecaprevir**, grazoprevir, paritaprevir, simeprevir, voxilaprevir).
- NS5A inhibitors that inhibit the NS5A protein, which is thought to play a role in both viral replication and assembly of HCV, although the precise molecular mechanisms of this function are uncertain (daclatasvir, elbasvir, ledipasvir, ombitasvir, **pibrentasvir**, velpatasvir).
- NS5B RNA-dependent RNA polymerase inhibitors inhibit the HCV RNA polymerase NS5B and come in two classes:
    - Nucleoside polymerase inhibitors (NPIs) which compete with nucleotides and cause chain termination during RNA replication (sofosbuvir).
    - Non-nucleoside polymerase inhibitors (NNPIs) which act directly on NS5B to inhibit RNA replication (dasabuvir).

Current standard-of-care utilizes multiple DAAs in combination (often fixed-dose combination regimens) to maximize SVR while limiting viral resistance and side effects. Regimens containing interferon and ribavirin are limited to patients without access to DAAs or in whom previous DAA therapy has failed. The choice of a specific regimen is based on the individual patient and is beyond the scope of this discussion; however, it involves a combination of HCV genotype, prior treatment experience, presence of HCV resistance mutations, and cirrhosis. Recently, the increased availability of multi-genotypic or pan-genotypic DAA regimens have greatly simplified selecting treatment regimens in adults.

Currently, there are no pan-genotypic ribavirin (RBV)-free regimens approved for use in HCV-infected individuals <18 years old. The combinations of ledipasvir (LDV)/sofosbuvir (SOF) and SOF + RBV are approved for use in adolescents, though neither combination covers all major genotypes alone. The only HCV therapy currently approved for use in pediatric patients < 12

years old in the U.S. is the combination of pegylated interferon (IFN) and RBV. This IFN + RBV regimen is frequently associated with influenza-like illness, headache, gastrointestinal symptoms, neutropenia, and anemia. DAAs such as LDV/SOF have allowed adult and adolescent patients achieve significantly higher rates of sustained virologic response (SVR) with significantly fewer side-effects.

Supplemental NDA application S-6 requests approval of GLE/PIB for treatment of chronic HCV GT 1, 2, 3, 4, 5, or 6 without cirrhosis or with compensated cirrhosis in pediatric patients 12 years of age and older. The data discussed are derived from Part 1 of protocol M16-123: An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection. Part 1 includes adolescent subjects ≥ 12 years of age treated with the adult regimen. If approved, GLE/PIB would be the first pangenotypic, ribavirin free DAA regimen available for children with chronic HCV infection.

2. Regulatory Background

Glecaprevir, an HCV nonstructural viral protein 3/4A (NS3/4A) protease inhibitor, and pibrentasvir, an HCV nonstructural viral protein 5A (NS5A) inhibitor, are denoted "next generation" compounds because each demonstrated potent antiviral activity against GT1 through GT6 in vitro and have a high genetic barrier to resistance with no or little loss of potency against common resistance-associated substitutions. Additive or synergistic in vitro anti-HCV activity were demonstrated with the combination of GLE and PIB.

On August 3, 2017, MAVYRET, a fixed-dose combination of GLE/PIB, was approved for two indications: 1) adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; 2) adult patients with HCV GT1 infection who previously have been treated with a regimen containing either an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. The duration of treatment with GLE/PIB in adults was based on a combination of factors including prior treatment experience, HCV genotype, and the presence or absence or cirrhosis as detailed in **Table 1**:

Table 1: GLE/PIB Duration Determination

Treatment-Naïve Patients			
HCV Genotype		**Treatment Duration**	
		No Cirrhosis	**Compensated Cirrhosis (Child-Pugh A)**
1, 2, 3, 4, 5, or 6		8 weeks	12 weeks
Treatment-Experienced Patients			
		Treatment Duration	
HCV Genotype	**Patients Previously Treated with A Regimen Containing:**	**No Cirrhosis**	**Compensated Cirrhosis**
1	An NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks
	An NS3/4A PI without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	Interferon, ribavirin, and/or sofosbuvir, but no prior treatment with NS3/A PI or NS5A inhibitor	8 weeks	12 weeks
3	Interferon, ribavirin, and/or sofosbuvir, but no prior treatment with NS3/A PI or NS5A inhibitor	16 weeks	16 weeks

Source: MAVYRET prescribing information

To better understand the potential use of GLE/PIB regimens in pediatric patients, PREA PMR 3246-1 was issued with the original NDA approval and requests the following: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of glecaprevir and pibrentasvir in pediatric subjects 3 through less than 18 years of age with chronic hepatitis C infection. A waiver was granted for the pediatric population younger than 3 years of age "on the grounds that the specific medicinal product does not represent a significant benefit over existing treatment for pediatric patients" in this age group. Additionally, while the risk of chronic HCV infection is high with perinatal transmission, there is a considerable rate of spontaneous clearance in children less than 3 years of age that limits the urgency to treat in this age range.

Study M16-123 was developed in accordance with the agreed initial Pediatric Study Plan (iPSP) and Pediatric Investigational Plan (PIP) for GLE/PIB for the treatment of HCV infection (US IND Number 127416, Reference ID: 3959249, European Medicines Agency [EMA] reference EMEA-001832-PIP01-15). The Pediatric Committee (PDCO) of the EMA issued a positive decision on the PIP for GLE/PIB on June 14, 2016. Similarly, on July 15, 2016, FDA confirmed

its agreement with the iPSP for GLE/PIB. The study design was also influenced by Japanese study requirements outlined by the Pharmaceuticals and Medical Devices Agency (PMDA). FDA also issued a Written Request (NDA 209394, Sequence 0064, January 23, 2018) for pediatric studies in children 3 to < 18 years of age.

The results from study M16-123 Part 1, which evaluated the adult GLE/PIB formulation in children 12 to < 18 years of age, has been submitted as a partial response to the PREA PMR. Part 2, which is ongoing in children 3 to < 12 years of age, is evaluating a pediatric formulation comprised of (b) (4) Data from this cohort will be submitted at a later date to complete the PREA PMR and Written Request requirements.

With this submission, AbbVie requested priority review designation. The only HCV treatments currently FDA-approved for adolescents include LDV/SOF (GT 1, 4, 5, 6), SOF + RBV (GT 2, 3) or a combination of IFN administered by subcutaneous injection in combination with oral RBV. The IFN/RBV regimen requires a long treatment course (24 – 48 weeks depending on HCV GT) which has been demonstrated to be poorly tolerated. In addition, SVR rates in subjects with HCV GT 1, 4, 5, and 6 were only 54%[3]. LDV/SOF and SOF +RBV provide an effective and well tolerated regimen in this age group but neither regimen provides pangenotypic coverage. GLE/PIB provides the potential for HCV GT1-6 cure with a once daily medication given for 8 to 16 weeks for most patients. In summary, the Division granted AbbVie priority review designation because GLE/PIB offers a major advancement in the treatment of chronic HCV infection in the adolescent patient population with regards to safety, efficacy, and tolerability.

3. CMC/Device

For a description of the product quality assessment, please refer to the original GLE/PIB NDA 209394 review. No new product quality information is included with S-6 because the study evaluated the currently marketed adult formulation. No quality inspections of manufacturing and testing sites were required as these sites were inspected during review of the original GLE/PIB NDA.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology data for GLE and PIB were extensively reviewed in the original GLE/PIB NDA review. No new nonclinical pharmacology/toxicology information is included with S-6.

5. Clinical Pharmacology/Biopharmaceutics

The basis of approval of MAVYRET in adolescent subjects is extrapolation of efficacy from adult subjects by matching systemic exposures of GLE and PIB between adults and adolescents with HCV infection.

Please see the Clinical Pharmacology review by Dr. Su-Young Choi and colleagues for complete details of the clinical pharmacology and pharmacometrics evaluation. In short, data from study M16-123 Part 1 demonstrate that the mean systemic exposures of GLE and PIB are comparable between adults and adolescent subjects when the adult dosing regimen of MAVYRET is administered to adolescent subjects. The results are summarized in **Table 2**.

Table 2: Comparison of the Mean Pharmacokinetic Parameters of GLE and PIB After Administration of 300/120 mg Once Daily to Adolescents and Adult Subjects with Chronic Hepatitis C

		GLE			PIB		
Population	N	C_{max} (ng/mL)	AUC_{24} (ng·hr/mL)	C_{min} (ng/mL)	C_{max} (ng/mL)	AUC_{24} (ng·hr/mL)	C_{min} (ng/mL)
Adolescents, Intensive	14*	1040 (66%) [245, 3400]	4790 (67%) [1580-16300]	3.79 (61%) [0, 8.9]	174 (28%) [72, 248]	1380 (31%) [530, 2090]	15.0 (43%) [4.7, 28]
Adolescents, Intensive	17[$]	662 (83%) [57, 3400]	3222 (84%) [473, 16300]	3.0 (67%) [0, 8.9]	133 (47%) [34, 248]	1095 (46%) [329, 2090]	13 (52%) [2.1,28]
Adolescents, PopPK	47	525 (170%) [18, 7801]	4504 (168%) [100, 80500]	6.3 (480%) [0, 86]	98 (43%) [18, 275]	1375 (62%) [300, 3230]	13.2 (55%) [0.101, 78.0]
Adults, PopPK	1804[#]	597 (114%) [127, 3322]	4800 (122%) [123, 297000]	4.86 (374%) [1.60, 288]	110 (49%) [49, 238]	1430 (57%) [148, 14200]	7.06 (110%) [5.6, 74]

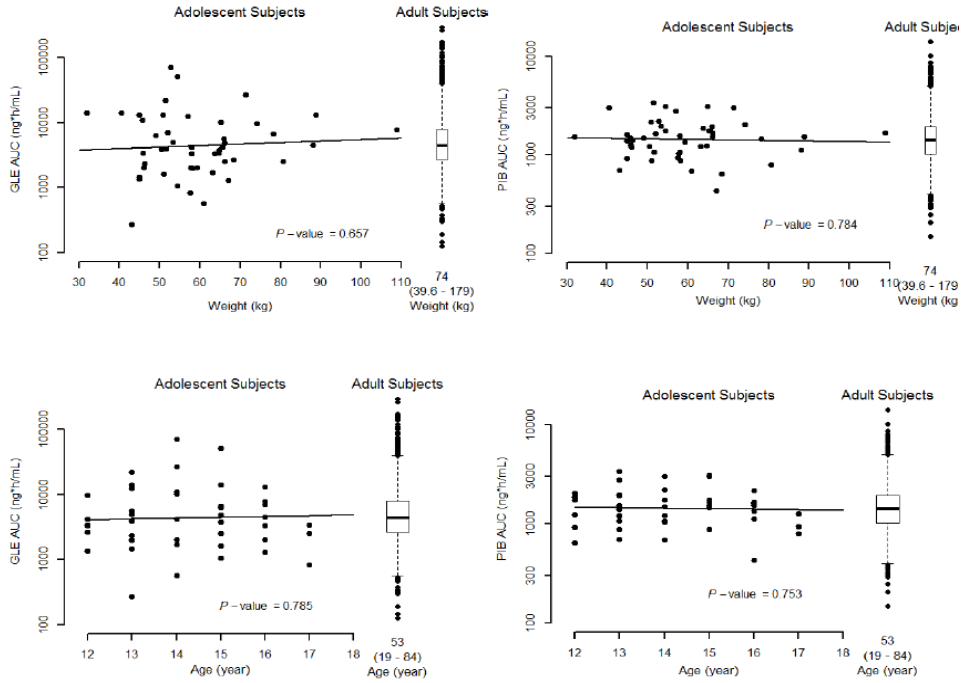
Data are presented as geometric mean (%CV) [min-max]
Data from three subjects who had extremely low GLE/PIB concentrations (i.e., outliers) were excluded in the analyses.
$: Data from all subjects in the intensive PK group including the three outliers
PopPK results: Intensive PK data from three outlines were excluded, but sparse PK data from the same subjects were included as sparse samples were collected via venipuncture.
#: Data were submitted in the original NDA
Source: Clinical Pharmacology Review for NDA 209394/S6

As noted in Table 2, three subjects in the intensive PK groups had significantly lower exposures of GLE and PIB (Subjects (b) (6)). Despite the lower concentrations (90% for GLE and 70% for PIB), all three subjects achieved SVR12. Intrinsic and extrinsic factors were examined as a cause, but when nothing unique was found, study and analysis procedures were examined. All three subjects were from the same study site (Children's Hospital of Pittsburgh) and these were the only subjects enrolled in the intensive PK cohort at this site. This suggested potential methodological issues affecting the PK results and prompted both the Applicant and FDA's Office of Scientific Investigations (OSIS) to perform clinical site inspections at the site. The only notable finding was that PK samples were drawn from an intravenous catheter to avoid repeated venipuncture. The clinical pharmacology review team agrees with the Applicant that it is reasonable to exclude exposure data from these three subjects as samples were potentially diluted with solution in the IV line.

Age and Weight

The Applicant evaluated the relationships between subjects' age/weight and model-predicted steady-state GLE and PIB AUC24 from population pharmacokinetic analyses. As demonstrated in Figure 1, no notable trends were observed.

Figure 1: Relationships Between Model-Predicted GLE and PIB Steady-State AUC24 and Age and Weight



Source: Applicant's population PK report, Page 51, Figure 11

Race
Four Japanese subjects were enrolled in Part 1 of study M16-123. Overall, model-predicted GLE and PIB steady-state exposures in Japanese adolescents were 87% and 36% higher respectively, than the exposures in non-Japanese adolescents. However, the predicted exposures in Japanese adolescents still fell within the exposure ranges from adults in global studies and Japanese HCV-infected adults. Given the favorable risk/benefit profile in Japanese HCV-infected adults, such higher exposures in Japanese adolescents are not considered clinically meaningful.

Inspections
In addition to the clinical site inspection referenced above, OSIS conducted a bioanalytical site inspection (AbbVie). The OSIS reviewers determined the data are acceptable to be used to support the approval of the proposed dosing regimens. Please refer to the full OSIS site inspection report for AbbVie, Inc. (North Chicago, IL) completed by Yiyue Zhang, Ph.D. on February 28, 2019.

6. Clinical Microbiology

Please refer to the full Clinical Microbiology review by Patrick Harrington, Ph.D. Briefly, the efficacy supplement is considered approvable from a Clinical Virology perspective based on the high efficacy of GLE/PIB observed in adolescent subjects in Part 1/Cohort 1 of M16-123 (SVR12=47/47 [100%]). No changes were proposed for Section 12.4 Microbiology of the MAVYRET prescribing information, which is acceptable to the reviewer given the limited resistance data included for this supplement.

Sample sizes were not adequate to assess efficacy in the adolescent population across all key HCV subgroups (e.g., GT3, treatment-experienced), and certain subgroups included in the approved indication were not represented (e.g., patients with cirrhosis, prior DAA experience, or HCV GT5 or GT6). Nevertheless, the efficacy and resistance characteristics of GLE/PIB are anticipated to be similar in adults and children, provided drug exposures are comparable. The relatively limited data from Part 1/Cohort 1 of M16-123 are sufficient to confirm GLE/PIB is reasonably effective in the adolescent population.

7. Clinical/Statistical - Efficacy

Efficacy Summary
As discussed in Section 5, pharmacokinetic data provide the pivotal data to support approval of the currently marketed GLE/PIB formulation for adolescent patients. This section summarizes the SVR12 data for Study M16-123, which provide supportive evidence of efficacy.

Extrapolation of efficacy for HCV DAAs such as GLE/PIB can be made based on the presumption that the course of chronic HCV disease and the effects of the drugs are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). DAVP agrees that HCV disease in pediatric subjects is similar but not identical to adult HCV

disease, noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for young children, in contrast to adolescent and adult subjects in whom injection drug use are the primary modes of transmission. Once infected, the pathophysiology HCV disease is similar in adult and pediatric subjects, although disease progression (e.g., cirrhosis, hepatocellular carcinoma, liver failure) occurs more slowly in children, largely because duration of infection appears to be an important factor affecting disease progression. Comorbid conditions such as underlying liver disease and alcohol or recreational drug use are also less common among children with HCV, which also contributes to slower disease progression during childhood.

For both children and adults, response to treatment of chronic HCV infection is measured by SVR12 (virologic cure). Several studies have shown achievement of SVR is associated with improvement of hepatic and extrahepatic manifestations, thereby improving overall health status. Consequently, treatment recommendations are very similar across all age groups for whom DAAs are available[4].

The submitted data demonstrate that administration of GLE/PIB 300mg/120mg (given as three 100mg/40mg tablets once daily) in pediatric participants ages ≥12 to <18 years with HCV GT 1, 2, 3, or 4 infection was efficacious. One hundred percent of participants enrolled in M16-123 achieved SVR 12. No participants experienced virologic breakthrough or viral relapse. HCV GT does not affect GLE/PIB pharmacokinetics and previous trials in adults have demonstrated that equivalent GLE/PIB exposure is efficacious in adults with chronic HCV GT 5 and 6 and adults with compensated cirrhosis.

7.1 Review Strategy

The clinical reviewer used the Applicant's ADaM datasets to analyze safety and efficacy data. Unless otherwise specified, all analyses included in this review were performed by the clinical reviewer using JReview software.

7.2 Indication

S-6 requests approval of GLE/PIB for (b) (4)

(b) (4)

7.3 Study Design

Study M16-123 is an ongoing Phase 2/3, open-label, multicenter study to evaluate the PK, efficacy, and safety of GLE/PIB for 8, 12, or 16 weeks in HCV GT1-GT6-infected pediatric subjects ≥ 3 to less than 18 years of age, with or without compensated cirrhosis, with or without human immunodeficiency virus (HIV) coinfection, who were either treatment-naïve (TN), treatment-experienced (TE) to IFN with or without RBV or TE to sofosbuvir (SOF) plus RBV with or without IFN. The study is divided into 2 parts.

- Cohort 1: HCV GT1 – GT6 infected adolescent subjects 12 to < 18 years old who were willing to swallow the adult formulation of GLE/PIB (n=47 including 17 subjects who provided intensive PK samples).
- Cohort 2-4: HCV GT1 - GT6 infected pediatric subjects divided into 3 groups based on age: 9 to < 12 years (Cohort 2), 6 to < 9 years (Cohort 3), and 3 to < 6 years (Cohort 4). Approximately 66 subjects will be enrolled across the 3 cohorts. Recruitment is ongoing in these groups and results are not available in the current submission.

The primary objectives of the study are to:
- Assess the steady state area under the concentration-time curve (AUC), and to assess the pharmacokinetics (PK) of GLE/PIB in pediatric subjects following multiple dosing by age group
- Evaluate the safety and tolerability of GLE/PIB by age group, cirrhosis status, and across all subjects.
- Evaluate the percentage of subjects with sustained virologic response for 12 weeks post-treatment (SVR12) in HCV GT1 – GT6 infected pediatric subjects

Dose selection for pediatric participants targeted systemic exposures similar to those observed in adults at the marketed dose. All participants were treated with the dose and duration marketed for adults in their respective country (300mg/120mg GLE/PIB daily for 8, 12, or 16 weeks depending on GT, prior treatment experience, and cirrhosis).

Subjects in the intensive pharmacokinetic (IPK) portion had to be HCV treatment-naive and HIV-negative, and the HCV genotype must have been identified. These subjects were specified to complete the EMA PIP measures. Subjects in the IPK portion are specified to take either 8 or 12 weeks of treatment, depending on their cirrhosis status and geographical location.

The non-IPK safety/efficacy portion of both Part 1 and Part 2 include pediatric subjects with or without compensated cirrhosis who were TN or TE (prior IFN, RBV or SOF exposure), with or without HIV-1 coinfection, and could include subjects with mixed or indeterminate HCV genotype. These subjects were added to fulfill the iPSP measures. Subjects in the non-IPK safety/efficacy portion of the study are specified to take 8, 12, or 16 weeks of treatment depending on their HCV genotype, prior treatment experience, cirrhosis status, and geographical location. All subjects will be followed for 144 weeks after the end of treatment.

7.4 Demographics and Clinical Characteristics

Forty-eight participants were enrolled in 8 countries and 47 received study medication (ITT population). The largest proportion of subjects was from the United States (38.3%) and 23.4% of subjects were HCV treatment-experienced. Most of the trial participants were white (74.5%) and non-Hispanic/Latino (89.4%) however minority populations were included in the trial: 8.5% of participants were black/African-American, 12.8% were Asian, 2.1% multi-racial, and 10.6% were Hispanic/Latino. Select demographics of the trial population are summarized in **Table 3**.

Table 3: Demographics			
Characteristic	**Treatment Experienced n=11**	**Treatment Naïve n=36**	**Total Participants n=47**
Gender			
Male	4 (8.5%)	17 (36.2%)	21 (44.7%)
Female	7 (14.9%)	19 (40.4%)	26 (55.3%)
Race			
White	8 (17.0%)	27 (57.4%)	35 (74.5%)
Asian	2 (4.3%)	4 (8.5%)	6 (12.8%)
Black/African-American	0	4 (8.5%)	4 (8.5%)
Multiple	1 (2.1%)	1 (2.1%)	2 (4.3%)
Ethnicity			
Hispanic or Latino	2 (4.3%)	3 (6.4)	5 (10.6%)
Not Hispanic or Latino	9 (19.1%)	33 (70.2%)	42 (89.4%)
Age (Years)			
Mean	14.5	14.2	14.3
Median	15	14	14
Range	13-16	12-17	12-17
Country			
Belgium	1 (2.1%)	2 (4.2%)	3 (6.4%)
Canada	0	4 (8.5%)	4 (8.5%)
Germany	1 (2.1%)	3 (6.4%)	4 (8.5%)
Japan	1 (2.1%)	3 (6.4%)	4 (8.5%)
Russian Federation	1 (2.1%)	1 (2.1%)	2 (4.3%)
Spain	4 (8.5%)	3 (6.4%)	7 (14.9%)
United Kingdom	2 (4.3%)	3 (6.4%)	5 (10.6%)
United States	1 (2.1%)	17 (36.3%)	18 (38.3%)

Source: Trial M16-123 demographics dataset

The majority (93.6%) of enrolled participants weighed ≥ 45 kg at baseline and all 3 participants who weighted < 45 kg were treatment-naïve. Only one participant weighed ≤ 35 kg.

Most participants enrolled in this trial were infected with HCV GT1 (78.8%) and were infected with HCV GT 1a (51.1%) vs HCV GT 1b (27.7%). No subjects were infected with HCV GT5 or GT6. Of the 11 (23.4%) participants who were treatment-experienced, all had been previously treated with IFN and RBV. No participants had been previously treated with SOF nor did any have cirrhosis. Few subjects were coinfected with HCV and HIV. Select baseline clinical characteristics of the trial population are summarized in **Table 4**.

Table 4: Baseline Clinical Characteristics			
Characteristic	**Treatment Experienced n=11**	**Treatment Naïve n=36**	**Total Participants n=47**
Weight			
Weight in kg	60.8	58.7	59.2
(mean/median/range)	54.4	58.0	57.7
	46-88.8	32-108.9	32-108.9
Weight ≥ 45 kg	11 (23.4%)	33 (70.2%)	44 (93.6%)
Weight < 45 kg	0	3 (6.4%)	3 (6.4%)
BMI			
BMI kg/m^2	24.4	21.9	22.5
(mean/median/range)	22.4	21.0	21.7
	18.5-42.2	16.3-34.1	16.3-42.2
BMI < 30 kg/m^2	9 (19.1%)	35 (74.5%)	44 (93.6%)
BMI ≥ 30 kg/m^2	2 (4.3%)	1 (2.1%)	3 (6.4%)
Hepatitis C RNA level			
RNA IU/mL (x 10^6)	3.5	2.63	2.75
(mean/median/range)	0.97	1.95	1.60
	0.20-15.30	0.04-13.70	0.04-15.30
RNA ≥ 800,000 IU/mL	6 (12.8%)	22 (46.8%)	28 (59.6%)
RNA < 800,000 IU/mL	5 (10.6%)	14 (29.8%)	19 (40.4%)
Hepatitis C GT			
1A	5 (10.6%)	19 (40.4%)	24 (51.1%)
1B	2 (4.3%)	11 (23.4%)	13 (27.7%)
2	0	3 (6.4%)	3 (6.4%)
3	3 (6.4%)	1 (2.1%)	4 (8.5%)
4	1 (2.1%)	2 (4.3%)	3 (6.4%)
5	0	0	0
6	0	0	0
Cirrhosis			
No known cirrhosis	11 (23.4%)	36 (76.6%)	47 (100%)
Compensated cirrhosis	0	0	0
Uncompensated cirrhosis	0	0	0
Prior Treatment Type			
IFN-based	11 (23.4%)	36 (76.6%)	47 (100%)
SOF-based	0	0	0
HCV/HIV Coinfection			
Yes	0	2 (4.3%)	2 (4.3%)
No	11 (23.4%)	34 (72.3%)	45 (95.7%)

Source: Trial M16-123 Subject-Level Analysis Dataset

7.5 Participant Disposition

Trial retention was high with one participant being enrolled who did not complete the study. Subject (b)(6) was enrolled but never received a dose of study drug and was not included in the ITT or safety populations. Forty-seven participants (100%) completed study treatment and all achieved SVR12.

While no participants were excluded from M16-123 Part 1 for protocol violations, there were three subjects considered to have protocol deviations:

- Subject (b)(6) took Sinupret for a sore throat for 5 days while receiving GLE/PIB treatment. Sinupret is an herbal medication which is not permitted per protocol while receiving GLE/PIB treatment. No significant DDIs were identified with co-administration of Sinupret.
- Subject (b)(6) completed study drug and then 10 days post-treatment, participant took Plantil (single dose). Plantil is an herbal medication which is not permitted per protocol for 14 days following discontinuation of GLE/PIB. No significant DDIs were identified with administration of Plantil.
- Subject (b)(6) was instructed to swallow the adult formulation of GLE/PIB whole at Day 1 visit and was willing and able to swallow the tablets. At the Week 4 visit, the participant notified the study site that they had been cutting the tablets in half at home. The subject confirmed that the entire 300/120 mg dose was taken daily, and no doses were missed.

The reviewers agree with the sponsor's assessment that none of the protocol deviations are likely to have affected the study outcome or interpretation of the study results or conclusions.

7.6 Analysis of Primary Endpoint

The primary efficacy endpoint of trial M16-123 was SVR 12 weeks after stopping study treatment (SVR12) for all enrolled and treated participants. One hundred percent of enrolled participants achieved SVR12 and no participants experienced on-treatment virologic failure or relapse (**Table 5**). No participants were lost to follow-up.

Table 5: Sustained Virologic Response after 12 Weeks of Treatment (SVR12)

	Treatment Experienced n=11	Treatment Naïve n=36	Total Participants n=47
Achieved SVR12	11 (100%)	36 (100%)	47 (100%)
Outcome for Subjects without SVR			
On-Treatment Virologic Failure	0	0	0
Relapse	0	0	0
Lost to Follow-up	0	0	0

Source: Trial M16-123 Efficacy Outcomes and Related Covariates Dataset

7.7 Analysis of Secondary Endpoints

The secondary efficacy endpoints for M16-123 included on-treatment virologic failure, viral relapse, and viral reinfection. No participants experienced virologic failure, relapse or reinfection.

7.8 Race, Ethnicity, and Sex

Because there were no participants who experienced viral relapse or viral breakthrough, formal subpopulation analyses were not conducted to assess for differences in efficacy based on race, ethnicity, or sex.

7.9. Weight

Although participation in Part 1 of trial M16-123 was limited to participants weighing ≥ 45 kg, patients >12 years of age could be enrolled below this threshold based on approval by the treating physician. Three patients (6.4%) weighed < 45 kg at enrollment and one (2.1%) weighed < 35 kg. All 3 participants who weighed < 45 kg at baseline achieved SVR12.

8. Safety

Safety Summary
Results from M16-123 demonstrate that GLE/PIB was safe and well-tolerated in adolescents. Overall, the adverse events observed were similar to those observed in adult clinical trials. Subgroup analyses did not identify any populations at greater risk for adverse events; however, this assessment was limited by the small sample size in some demographic groups.

8.1. Methods

Forty-seven of the forty-eight enrolled participants in trial M16-123 were included in the safety analysis of GLE/PIB in pediatric participants ages ≥ 12 to < 18 years who were treated with the dose and duration marketed for adults in their respective country of residence: 300mg/120mg GLE/PIB daily for 8, 12, or 16 weeks depending on GT, prior treatment experience, and

cirrhosis. One patient discontinued the study prior to receiving a dose of study medication and was not included in the safety population. All other participants completed treatment and follow-up.

Adverse events (AEs) are defined as any unfavorable and/or unintended sign, symptom, or disease temporally associated with GLE/PIB regardless of causality. Adverse drug reactions (ADRs) are defined as AEs deemed to be at least possibly related to GLE/PIB by the investigator's causality assessment.

AEs are coded using MedDRA 20.1. The sNDA S-6 submission includes the AE dictionary files that consist of all verbatim and the preferred/dictionary-derived terms. AbbVie's categorization of closely related events and coding of AE verbatim terms to preferred terms is appropriate.

Unless otherwise specified, all the analyses used to support this review were conducted with JReview software.

8.2 Adequacy of Safety Assessments

The safety monitoring plan implemented in trial M16-123 was adequate.

Study visits in the Treatment Phase occurred on Day 1 and at the end of weeks 1, 2, 4, 8, 12, and 16. Visits at the end of weeks 12 and 16 only applied to treatment-experienced participants on longer durations of treatment. Each follow-up visit included: a focused physical examination with vital signs; an assessment of AEs, medication adherence, and concomitant medications; and safety and virology laboratory studies. Post-treatment follow-up is planned to continue through 144 weeks after last dose of study medication (post-treatment week 4, 12, 24, 48, 96 and 144 follow-up visits) and includes vital signs, weight/height/BMI checks, longitudinal Fibrotest and AST-platelets ratio index (APRI), HCC assessment (both liver ultrasound and alpha fetoprotein), concomitant medication assessment, AE assessment, and HCV RNA samples. At the time of this review, no patients have gone past the week 48 post-treatment assessment.

8.3 Major Safety Results

No major AEs or ADRs were reported. No deaths occurred during the study. No AEs led to premature discontinuation or to treatment interruption. No Serious AEs (SAEs) were reported. One Grade 3 AE of "increased depression" was reported in subject (b) (6). This subject also reported a Grade 2 AE of "suicidal ideation." Subject (b) (6) was reported to have AEs develop starting on Treatment Day 14 in relation to school bullying and both resolved follow referral to psychotherapy. This single Grade 3 AE was determined to be unrelated to GLE/PIB by investigators and given the nature and alternative explanation, the investigators' assessment of causality is reasonable.

8.4 Dropouts and Discontinuations.

No participants discontinued study drug or interrupted treatment with study drug due to an AE. All participants who started treatment went on to complete therapy. One participant was enrolled but was never given a dose of study drug (subject (b) (6)). No participants were lost to follow-up.

8.5 Common Adverse Events and Adverse Drug Reactions

This section summarizes the AEs and ADRs that occurred in trial M16-123.

Overall, 110 AEs occurred in 41 of 47 participants. Sixty-eight percent of participants experienced AEs with maximum Grade 1 toxicity and 34 percent of participants experienced AEs with maximum Grade 2 toxicity. A single patient experienced a Grade 3 toxicity as described in **Section 8.4**. The most common AEs fell under the following System Organ Classes: gastrointestinal, nervous system, respiratory, infections and infestations, and general disorders (**Table 6**).

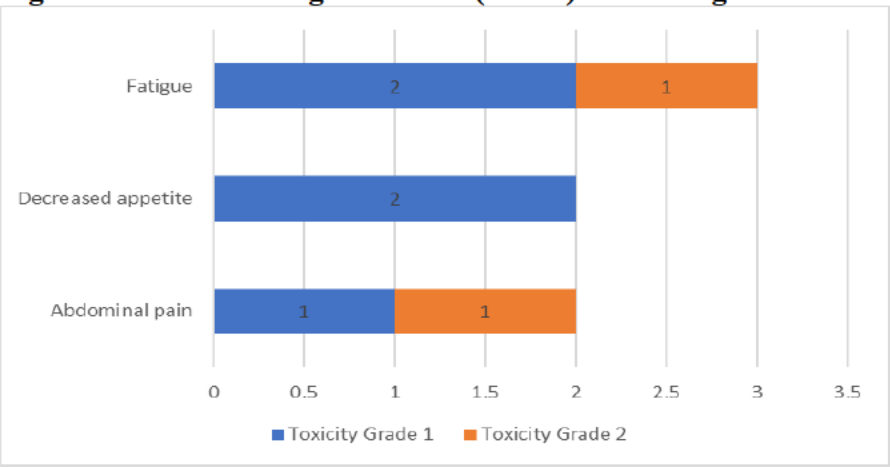
Table 6: AEs (Without Regard to Causality) ≥ 5% By System Organ Class

Body System or Organ Class	Dictionary Derived Term	Number of Participants (%) n=47
Gastrointestinal disorders	Diarrhea	3 (6.4%)
	Nausea	4 (8.5%)
	Vomiting	4 (8.5%)
General disorders and administration site conditions	Fatigue	5 (10.6%)
	Pyrexia	5 (10.6%)
Infections and infestations	Nasopharyngitis	12 (25.5%)
	Upper respiratory infection	9 (19.1%)
Nervous system disorders	Headaches	8 (17.0%)
Respiratory, thoracic and mediastinal disorders	Nasal congestion	4 (8.5%)
	Oropharyngeal pain	5 (10.6%)

Source: Trial M16-123 Adverse Events Analysis Dataset

Sixteen ADRs occurred in 9 participants. The majority of participants with ADRs experienced Grade 1 events and only 1 participant experienced Grade 2 ADRs. There were no Grade 3 or higher ADRs. As shown in **Figure 2**, the most common ADRs were fatigue (6.4%), decreased appetite (4.3%), and abdominal pain (4.3%).

Figure 2: Adverse Drug Reactions (ADRs) Occurring in >1 Participant



Source: Trial M16-123 Adverse Events Analysis Dataset

Compared to pooled adult safety data (M13-590, M15-464, M15-594, M14-867, M14-868, M14-172, M15-210) from the original Mavyret NDA clinical review, children experienced fewer treatment-related headaches, nausea and diarrhea while adults experience less abdominal pain and decreased appetite. Both populations reported similar levels of fatigue. All ADRs experienced by children in trial M16-123 were reported as Grade 1 or 2 intensity (**Table 7**).

Table 7: Adverse Drug Reactions occurring in ≥ 5% of Adults and/or Children receiving 8 to 16 weeks of GLE/PIB

Adverse Event	Adults Cirrhotic n=1,977	Adults Non-Cirrhotic n=288	Children n=47
Headache	13.5%	13.1%	0
Fatigue	14.9%	10.9%	6.4%
Nausea	8.3%	7.5%	0
Diarrhea	5.6%	3.5%	0
Abdominal Pain	2.1%	1.2%	4.3%
Decreased Appetite	2.4%	1.5%	4.3%

Source: Primary Clinical Review of NDA 209394 and Trial M16-123 Adverse Events Analysis Dataset

8.6 Laboratory Findings

Laboratory evaluations were assigned toxicity grades according to a severity scale established in the AbbVie M16-123 trial protocol (Toxicity Grade 0 (i.e. normal), 1, 2, 3, 4). Overall, there were 53 reported treatment-emergent laboratory abnormalities as shown below in **Table 8**. This table denotes participants who had a toxicity grade increase above their baseline value. Participants with stable or decreased toxicity grades throughout the study are not included as the laboratory anomaly was considered unrelated to study drug administration. Fifty-two of these abnormalities were maximum Grade 1 or 2 with the majority being Grade 1 (50 abnormalities).

There was a single reported Grade 3 laboratory abnormality of neutropenia that was present to a lesser degree prior to initiation of study drug and returned to baseline without stopping treatment. There were no reported Grade 4 abnormalities. Notable treatment-emergent laboratory events included elevated ALT, AST, and/or bilirubin that could represent treatment-emergent hepatic disease due to study drug and are discussed below in **Section 8.6.1**. The most common laboratory abnormalities were elevated alkaline phosphatase (13 participants, 28%) and hyperglycemia (16 participants, 34%), however, the clinical reviewer determined that these values are not clinically significant as they were all both mild (maximum toxicity grade 1) and transient. Mild-to-moderate alkaline phosphatase elevations (from bone sources) are common in pediatric patients who are growing and undergoing rapid bone remodeling and much less commonly related to underlying hepatic sources without other evidence of significant hepatic injury. Laboratory values not detailed in **Table 8** showed no significant elevations in toxicity grading over baseline values and include various hematologic parameters (activated partial thromboplastin time, absolute leukocyte count, hemoglobin, platelets), basic chemistry values (sodium, magnesium, potassium), and renal function (creatinine clearance, urinalysis). In general, the frequency and severity of laboratory abnormalities seen over the course of the trial are similar to those seen in adults.

Table 8: Grade 1-4 Hematology and Chemistry Laboratory Abnormalities (Maximum Grade over Baseline)

Parameter	Toxicity Grade	Result Range	Number (%) of Participants n=47
Lymphocytes (Absolute Lymphopenia)	1	600 to 650/mm^3	5 (10.6%)
	2	500 to < 600/mm^3	1 (2.1%)
	3	350 to < 500/mm^3	0
	4	< 350/mm^3	0
Neutrophils (Absolute Neutropenia)	1	1000 to 1300/mm^3	1 (2.1%)
	2	750 to < 1000/mm^3	1 (2.1%)
	3	500 to < 750/mm^3	1 (2.1%)
	4	< 500/mm^3	0
Creatine Kinase	1	3.0 to 6.0 x ULN	2 (4.3%)
	2	> 6.0 to 10.0 x ULN	0
	3	> 10.0 to 20.0 x ULN	0
	4	> 20.0 x ULN	0
Glucose (Hyperglycemia)	1	116 to 160 mg/dL	16 (34.0%)
	2	> 160 to 250 mg/dL	0
	3	> 250 to 500 mg/dL	0
	4	> 500 mg/dL	0
Glucose (Hypoglycemia)	1	55 to 64 mg/dL	5 (10.6%)
	2	40 to < 55 mg/dL	0
	3	30 to < 40 mg/dL	0
	4	< 30 mg/dL	0

Source: Trial M16-123 Lab Toxicity Grade Analysis Dataset

8.6.1 Liver Toxicity

Trial M16-123 included several AEs of special interest, however, none were found amongst the study population during the trial period. These AEs of special interest included:

- All AEs of HCC identified using the preferred terms of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent; treatment.
- Treatment-emergent hepatic decompensation/hepatic failure AEs, defined as ascites, hepatic encephalopathy, esophageal variceal bleeding, or spontaneous bacterial peritonitis.
- On treatment-hepatic laboratory parameters of interest
    - confirmed post-nadir ALT > 5 x ULN.
    - post-nadir ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN with direct/total bilirubin > 0.4.

As occurs in adults with chronic HCV, serum liver biochemistry elevations were common at baseline in the pediatric participants in trial M16-123. At baseline, 21 percent of participants had Grade 1-3 ALT values, 21 percent had Grade 1-3 AST values, and 13 percent had Grade 1 alkaline phosphatase elevations. No participants had bilirubin toxicity graded values at baseline. After initiation of GLE/PIB, 21 participants (45%) went from Grade 0 to Grade 1 at any time point in the study for a liver biochemistry toxicity grade as shown in **Table 9**. No participants experienced maximum Grade 2 or above changes in liver biochemistry studies.

Table 9: Grade 1-4 Hepatic Laboratory Abnormalities (Maximum Grade over Baseline)

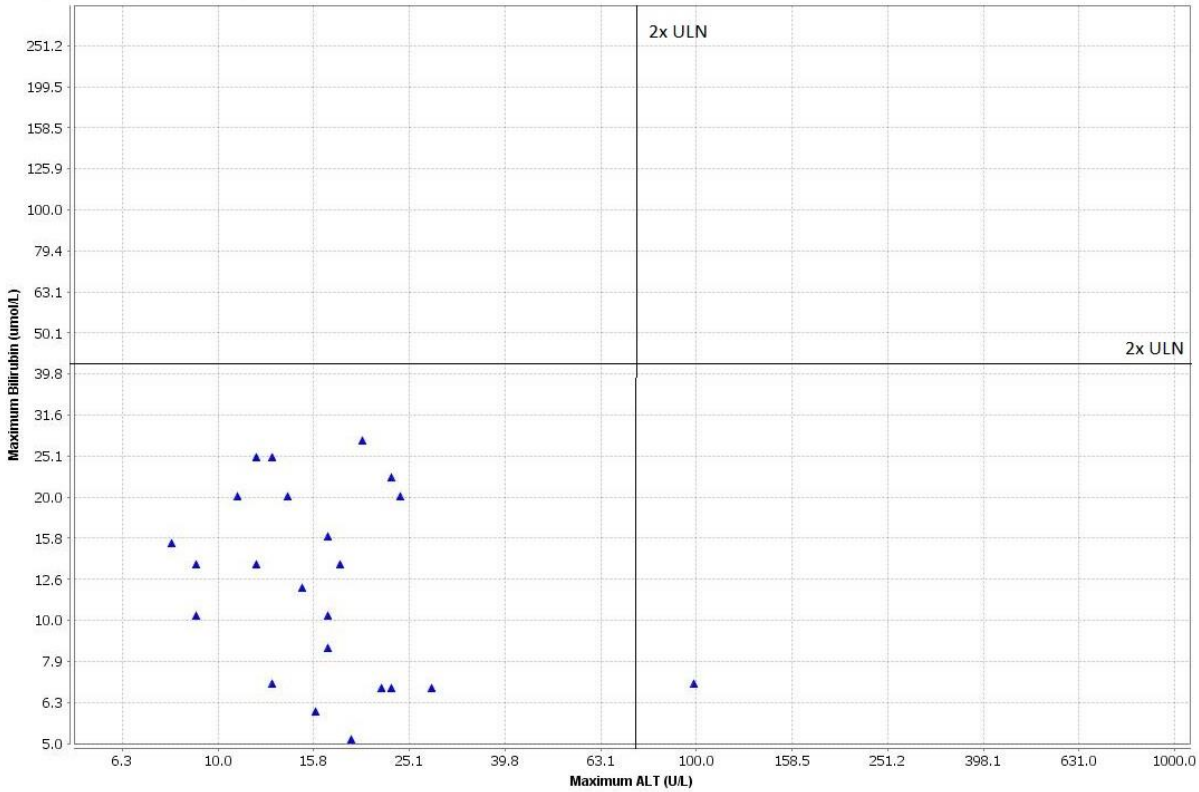
Parameter	Toxicity Grade	Result Range	Number (%) of Participants n=47
PT/INR	1	1.00 to 1.50 x ULN	1 (2.1%)
	2	> 1.50 to 2.00 x ULN	0
	3	> 2.00 to 3.00 x ULN	0
	4	> 3.00 x ULN	0
Alanine Aminotransferase (ALT/SGPT)	1	1.25 to 2.50 x ULN	1 (2.1%)
	2	> 2.50 to 5.00 x ULN	0
	3	> 5.00 to 10.00 x ULN	0
	4	> 10.00 x ULN	0
Aspartate Aminotransferase (AST/SGOT)	1	1.25 to 2.50 x ULN	2 (4.3%)
	2	> 2.50 to 5.00 x ULN	0
	3	> 5.00 to 10.00 x ULN	0
	4	> 10.00 x ULN	0
Alkaline Phosphatase	1	1.25 to 2.50 x ULN	13 (27.7%)
	2	> 2.50 to 5.00 x ULN	0
	3	> 5.00 to 10.00 x ULN	0

	4	> 10.00 x ULN	0
Bilirubin (Hyperbilirubinemia)	1	> 1.00 to 1.50 x ULN	4 (8.5%)
	2	> 1.50 to 2.50 x ULN	0
	3	> 2.50 to 5.00 x ULN	0
	4	> 5.00 x ULN	0

Source: Trial M16-123 Lab Toxicity Grade Analysis Dataset

As shown in **Figure 3** which compares maximum bilirubin and ALT values at any point in the post-baseline study period, no participants met criteria for Hy's Law. A single patient had a maximum ALT value >2x normal with a value of 99 U/L reported during week 2 of treatment with GLE/PIB. Her ALT had previously been noted as normal at baseline (24 U/L) and subsequently declined back to normal range by her next lab check at week 4 of treatment (38 U/L). This decline occurred without stopping study medication and all subsequent checks including week 8, post-treatment week 4 and post-treatment week 12 were stable/declining (22, 18, and 17 U/L, respectively). The clinical reviewer considered this elevation unrelated to study treatment.

Figure 3: Liver Toxicity in M16-123 (Hy's Law)



Source: Trial M16-123 Lab Hepatotoxicity Analysis Dataset

In summary, no new safety concerns related to liver toxicity in the adolescent population were identified.

8.7 Product-Specific Primary Safety Concerns

The Warnings and Precautions Section of the GLE/PIB label does not caution prescribers and patients for additional concerns except for risk of Hepatitis B Virus reactivation. Therefore, no additional product-specific primary safety concerns were studied in this pediatric supplement.

8.8 Growth and Development in Adolescents

Post-marketing commitment (PMR) 3246-1, which was issued at the time of GLE/PIB approval, stipulated that AbbVie conduct a study to evaluate PK, safety and treatment response in pediatric subjects 3 through less than 18 years of age. As part of this commitment, AbbVie conducted assessments of child growth parameters throughout the study period with plans to continue into a follow-up study that all participants are offered enrollment into. Because study M16-123 was of short duration and not powered to detect meaningful differences in growth parameters and because growth parameters are expected to be highly variable in this age group, the analyses described here are exploratory.

Height and BMI were assessed at baseline and at all study visits with plans to continue through post-treatment week 144. Overall, mean BMI increased by a z-score of 0.66 (SD 1.213) for all subjects by the final treatment visit. Female participants had a lower growth rate (mean of 15 mm/year) relative to male participants (mean of 43 mm/year) over the course of the treatment period. These values are within normal expected ranges for male and female adolescent growth; however, there is significant variation amongst gender and age-range, so conclusions cannot be drawn over such a short study time period.

8.9 Race, Ethnicity, and Gender

Subpopulation analyses were performed by the clinical reviewer to assess differences in safety between key groups. Because protocol M16-123 was not powered to detect differences between these individual populations, the analyses are exploratory. Race, ethnicity, and gender did not appear to influence the frequency or severity of adverse drug reactions. Race, ethnicity, and gender were also compared to all adverse events and did not appear to influence the frequency or severity of events. Only the adverse drug reaction analysis is detailed below for simplicity (**Table 10).**

Table 10: Adverse Drug Reactions by Race, Ethnicity, and Gender

Adverse Event	All n=47	Race & Ethnicity					Gender	
		White, non-Hispanic n=31	Hispanic n=5	Asian n=5	Black or African-American n=4	Multiple n=2	Male n=21	Female n=26
All Events	15 (31.9%)	13 (41.9%)	0	1 (20%)	0	1 (50%)	9 (42.3%)	6 (23.1%)
Abdominal distension	1 (2.1%)	0	0	0	0	1 (50%)	0	1 (3.8%)
Abdominal pain	2 (4.3%)	2 (6.5%)	0	0	0	0	1 (4.8%)	1 (3.8%)
Chills	1 (2.1%)	1 (3.2%)	0	0	0	0	1 (4.8%)	0
Crystal urine present	1 (2.1%)	1 (3.2%)	0	0	0	0	0	1 (3.8%)
Decreased activity	1 (2.1%)	1 (3.2%)	0	0	0	0	1 (4.8%)	0
Decreased appetite	2 (4.3%)	2 (6.5%)	0	0	0	0	1 (4.8%)	1 (3.8%)
Fatigue	3 (6.4%)	3 (9.7%)	0	0	0	0	1 (4.8%)	2 (7.7%)
Hyper-bilirubinemia	1 (2.1%)	1 (3.2%)	0	0	0	0	1 (4.8%)	0
Proteinuria	1 (2.1%)	1 (3.2%)	0	0	0	0	1 (4.8%)	0
Somnolence	1 (2.1%)	0	0	1 (20%)	0	0	1 (4.8%)	0
Vasculitic rash	1 (2.1%)	1 (3.2%)	0	0	0	0	1 (4.8%)	0

Source: Trial M16-123 Adverse Event Analysis Dataset

9. Subpopulations

The adult GLE/PIB development program included dedicated clinical trials in several subpopulations of patients including those with cirrhosis, HIV-1/HCV coinfection, advanced kidney disease, or receipt of a liver or kidney transplant. The FDA recommended studying these populations because it was not yet clear whether these clinical factors would affect the safety or efficacy of GLE/PIB. Thus far, as discussed in Dr. Larissa Stabinski's Primary Clinical Review and completed supplements, clinical trial results demonstrate a favorable risk/benefit assessment of GLE/PIB in these populations and provided the rational for expanding the indication for use in adults.

This section focuses on subpopulations that were unrepresented or represented in small numbers in Trial M16-123 and outlines the clinical review team's rationale for recommending inclusion

of pediatric patients with HCV GT 5 and 6, compensated cirrhosis, or HIV-1/HCV coinfection in this pediatric approval.

Cirrhosis

Cirrhosis is uncommon among children with chronic HCV. However, children with cirrhosis are at a high risk of disease progression without treatment. Clinical trials in adults demonstrated the safety profile of GLE/PIB in adults is similar over 12-16 weeks and the presence of cirrhosis did not have significant impact on safety. The presence of cirrhosis is not expected to alter PK exposures in children relative to adults where GLE/PIB has been previously found to be effective when given the appropriate durations.

Trial M16-123 was open to both treatment-naïve and treatment experienced pediatric participants with compensated cirrhosis, however, the trial did not enroll any participants with cirrhosis. The current Mavyret label includes a recommendation for 12 to 16 weeks of GLE/PIB for treatment of adult subjects with compensated cirrhosis based on a combination of HCV genotype and prior treatment experience. While no pediatric participants in the trial had cirrhosis, AbbVie was able to provide safety data from three children who were treatment experienced with HCV GT 3 and therefore received the longer duration of treatment that would be recommended for some cirrhotic patients (16 weeks of GLE/PIB). All three participants completed treatment, and none experienced any Grade 2-4 AEs, AEs leading to study drug discontinuation, serious AEs, or Grade 3-4 laboratory abnormalities.

Given the sufficient similarity in the natural history of chronic HCV disease between children and adults, and the similarities in the treatment and PK/pharmacodynamic (PD) relationship between adults and adolescents, extrapolation of efficacy between populations is possible provided that drug exposure is matched. GLE and PIB exposures have found to be comparable and data from the three trial participants completing 16 weeks of GLE/PIB, along with the safety data demonstrated over 8 weeks in the remainder of the cohort, support the safety of GLE/PIB in adolescents. Therefore, the clinical team recommends extending the pediatric approval to children with compensated cirrhosis.

HIV-1/HCV Co-infection

Among pediatric patients in the United States, HIV-1/HCV co-infection is rare and trial M16-123 included only 2 participants in this subgroup. Both participants completed treatment and achieved SVR12. No subjects experienced any Grade 2-4 AEs, AEs leading to study drug discontinuation, serious AEs, or Grade 3-4 laboratory abnormalities. Adult trials of GLE/PIB in adult participants with HIV-1/HCV co-infection have demonstrated high SVR12 rates comparable to subjects with HCV mono-infection with a similar safety profile. Data from HIV/HCV coinfected adults show that HIV-1 co-infection does not impact GLE/PIB response rates or safety profile. Therefore, the clinical team believes that GLE/PIB is safe and efficacious for use in children with HIV-1/HCV co-infection.

HCV GT 5 and 6

Infection with GT 5 or 6 is rare in the United States and although the trial was open to pediatric participants with these GTs, none were enrolled during this phase of the trial. HCV GT does not affect GLE/PIB exposure and previous trials in adults have demonstrated that equivalent GLE/PIB exposure is efficacious in adults with chronic HCV GT 5 and 6. Therefore, the submitted PK data are adequate to support the efficacy of MAVYRET for treatment of HCV GT 5 or 6 in adolescents.

Body Weight

As previously discussed, the paucity of safety data in children less weighing less than 45kg, coupled with the knowledge that a lower GLE/PIB dose may be sufficient to match systemic adult exposures, support inclusion of a minimum weight of 45 kg in the current regulatory action.

10. Advisory Committee Meeting

Not applicable.

11. Pediatrics

One PREA Postmarketing Requirement (PMR) for pediatric patients was issued in the initial approval letter for the GLE/PIB NDA 209394 dated August 3, 2017 .

4326-1 *Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of glecaprevir and pibrentasvir in pediatric subjects 3 through less than 18 years of age with chronic hepatitis C virus infection.*

The interim results of trial M16-123, which include data for pediatric participants ages 12-17, partially address PMR 4326-1. AbbVie plans to completely fulfill the above PMR by submitting data for pediatric participants ages 3-11 enrolled in Part 2 of trial M16-123 when available. The FDA waived the pediatric study requirements from birth to less than 3 years because necessary studies are highly impractical due to the high rate of spontaneous HCV clearance in that age group.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Based on the totality of the data presented and input from each of the review disciplines, the clinical review team recommends approval of GLE/PIB at the adult dose (100mg/40mg x 3 tablets, administered once daily) for the treatment of pediatric patients 12 years of age and older or weighting at least 45 kg with HCV GT 1, 2, 3, 4, 5 and 6 infection without cirrhosis or with compensated cirrhosis.

Risk Benefit Assessment

The overall risk benefit assessment is favorable for GLE/PIB. Efficacy and safety data presented in this sNDA do not alter the risk-benefit assessments made during the original NDA and supplemental reviews of GLE/PIB. One hundred percent of participants enrolled in M16-123 achieved SVR 12 and no participants experienced virologic breakthrough or viral relapse. Although interpretation of safety data is limited by the single arm, open-label trial design, no new safety concerns for adolescents emerged in the analysis of this clinical trial.

Therefore, approval is recommended for the indication to include pediatric participants ages ≥12 to <18 years and ≥ 45 kg with HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

The NDA contains no safety information necessitating REMS.

Recommendation for other Postmarketing Requirements and Commitments

The FDA will not issue any new PMR or PMC because of this review.

13. Labeling

Based on the reviewed adolescent patient data from Part 1 of M16-123, the Agency and Sponsor are engaged in ongoing discussions over labeling revisions. These currently include, but may not be limited to:

- Updates to Section 1 and 2 regarding new indications and regimens for patients aged 12 to 17 years.
- Adverse event safety data provided for adolescent population and comparison to previously available adult safety data in Section 6.
- Updated summaries of pediatric use in Section 8.4.

- Addition of efficacy results from adolescent subjects in M16-123 to Section 14.
- Updates to the corresponding sections of patient labeling.

14. References

[1] Gower E. Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of Hepatology. 2014;61(1 Suppl):S45 0 57.

[2] Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014;160(5):293-300.

[3] Manns MP, McHutchinson JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M-H, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet. 2001;358(9286):958-965.

[4] AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/search/benefits%20of%20treatment. Accessed March 29, 2019.

15. Other Relevant Regulatory Issues

Clinical Investigator Financial Disclosure Review Template.
Application Number: 209394 S-6

Submission Date(s): October 12, 2018

Applicant: AbbVie Inc.

Product: Mavyret (Glecaprevir/Pibrentasvir)

Reviewer: Nicholas Rister, MD

Date of Review: May 29, 2019

Covered Clinical Trial (Name and/or Number): M16-123

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 124		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of		

<table>
<tr><td colspan="3">investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 0

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>N/A ☒</td><td>No ☐ (Request details from applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☒ (section 1.3.4.1)</td><td>No ☐ (Request information from applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>N/A ☒</td><td>No ☐ (Request explanation from applicant)</td></tr>
</table>

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*. None of the 140 investigators had reportable financial disclosures or certifications of due diligence.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS S RISTER
03/29/2019 03:52:04 PM

PRABHA VISWANATHAN
03/29/2019 04:16:46 PM