U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209394
Supplement #:	S006
Drug Name:	Mavyret™ (Glecaprevir/Pibrentasvir), 100 mg / 40 mg tablets
Indication(s):	(b) (4) [redacted]
Applicant:	AbbVie, Inc.
Date(s):	Received: 10/31/2018 Filing Date: 11/30/2018 Primary Review Due Date: 3/31/2019 PDUFA: 4/30/2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV (DBIV)
Statistical Reviewer:	Therri Usher, PhD
Concurring Reviewers:	Thamban Valappil, PhD
Medical Division:	Division of Antiviral Products (DAVP)
Clinical Team:	Nicholas Rister, MD (Clinical Reviewer) Prabha Vishwanathan, MD (Cross-Disciplinary Team Leader) (DAVP Division Lead)
Project Manager:	Alicia Moruf, PharmD
Keywords:	HCV, labeling, open-label, pediatric population

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The applicant (AbbVie) submitted a supplemental New Drug Application (sNDA) for Mavyret, which was approved on August 3, 2017 for the treatment of chronic Hepatitis C virus (HCV) genotypes (GT) 1, 2, 3, 4, 5, and 6 in treatment-naïve and treatment-experienced adult patients without cirrhosis or with compensated cirrhosis. It was also approved for patients with HCV GT 1 infection who have previously been treated with a regimen containing a HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. The current sNDA is an efficacy supplement that proposes to update Mavyret's USPI based on results from Part 1 of Trial M16-123 (DORA), including an expansion of Mavyret's current indication to include adolescents 12 years and older.

DORA is a single-arm, open-label, multicenter, multi-part Phase 2/3 trial whose primary objectives include assessing the steady state area under the concentration-time curve, pharmacokinetics, safety, and efficacy of Mavyret in pediatric subjects. Part 1 enrolled 47 adolescent patients aged 12 to < 18 years of age who were willing to swallow the adult formulation of Mavyret. The subjects were HCV-infected subjects with GT 1, 2, 3, or 4, with or without HIV coinfection, who did not have cirrhosis and who were either treatment-naïve or treatment-experienced to interferon with or without sofosbuvir or ribavirin. Treatment duration was defined for each subject according to HCV genotype, cirrhotic status, HCV treatment experience, and geographical location, such as is done in adults.

The overall SVR12 rate (95% CI) was 100% (92.4%, 100%). No subjects experienced virologic failure. While the sample size for Part 1 of DORA was limited, the observed efficacy in adolescent subjects appears to be strong and consistent with efficacy in adult subjects. Therefore, there is sufficient evidence of efficacy to support evidence of safety in the adolescent population and comparable PK parameters to the adult population. It is the recommendation of the statistical review team that this sNDA be approved.

2 INTRODUCTION

2.1 Overview

Mavyret™ (Glecaprevir/Pibrentasvir [GLE/PIB]) 300/120 mg once daily (QD) was approved on August 3, 2017 for the treatment of chronic Hepatitis C virus (HCV) genotypes (GT) 1, 2, 3, 4, 5, 6 in treatment-naïve and treatment-experienced adult patients without cirrhosis or with compensated cirrhosis. It was also approved for patients with HCV GT 1 infection who have previously been treated with a regimen containing a HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

DAVP approved a previous efficacy supplement NDA on August 6, 2018. The supplement updated the Mavyret USPI with information from studies M13-596 and M14-730, which assessed the safety and efficacy of Mavyret in the HCV/HIV-1 coinfected and liver/renal transplant patient populations, respectively.

The current submission is an efficacy supplement that proposes to update Mavyret's USPI based on results from Part 1 of Trial M16-123 (DORA), including an expansion of Mavyret's current indication to include adolescents 12 years and older. A summary of Part 1 of DORA is provided in Table 1.

Table 1: List of Trials Included in Review

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects	Study Population
DORA (Part 1)	Phase 2/3, single-arm, open-label, multicenter, multi-part	Subjects who were not HCV GT3-infected or are TN: GLE/PIB 300 mg/120 mg QD for 8 weeks (n=44) Subjects who were HCV GT3-infected and TE-PRS: GLE/PIB 300 mg/120 mg QD for 16 weeks (n=3)	144 weeks after the end of treatment	47	Adolescents 12 to < 18 years of age who were willing to swallow the adult formulation of Mavyret HCV GT1-6 infected, with or without compensated cirrhosis, with or without HIV coinfection, TN or TE-PRS

HCV: Hepatitis C virus, GT: genotype, TN: treatment-naïve, GLE/PIB: glecaprevir/pibrentasvir, QD: once daily, TE-PRS: treatment-experienced with regimens containing interferon, ribavirin, and/or sofosbuvir, HIV: human immunodeficiency virus
Source: reviewer created

The efficacy data from Part 1 of DORA serves as the basis of proof of efficacy for Mavyret in adolescent populations. The evidence of efficacy is considered supportive to the evidence of adequate safety and similar pharmacokinetic (PK) parameters in adolescents to what has been

observed in adults. The applicant has requested and received Priority Review Designation for this sNDA.

2.2 Data Sources

The application was submitted electronically and can be found on the following FDA network drive: \\cdsesub1\evsprod\NDA209394\0085. The clinical study report and datasets for Part 1 of DORA can be found in the m5 folder.

Both SDTM and ADaM datasets were submitted. The SDTM and ADaM datasets, as well as the programs used to create them, can be found in the tabulations and analysis fodders at the following path, respectively: \\cdsesub1\evsprod\NDA209394\0085\m5\datasets\m16-123.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets is sufficient for review. From the SDTM datasets, the reviewer was able to recreate the observations in the ADaM datasets for the primary efficacy endpoint, sustained virologic response at Post-Treatment Week 12 (SVR12). From the ADaM datasets, the reviewer recreated and confirmed the applicant's calculations.

An adeffout.xpt data file for Part 1 of DORA was included in the submission and formatted in accordance with the FDA guidance, "Efficacy Data Submission in ADaM Conversion for HCV Drugs". Little data processing was required from the ADaM data sets.

Additionally, the applicant provided the statistical analysis plan and protocol for DORA in the submission. The applicant briefly acknowledged its methods of data quality assurances in the protocol for DORA. Randomization schemes and information regarding blinding were not included as DORA is a nonrandomized, open-label trial.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

DORA is a single-arm, open-label, multicenter, multi-part Phase 2/3 trial to assess the pharmacokinetics, safety, and efficacy of Mavyret in pediatric subjects who were infected with HCV GT1-6, with or without compensated cirrhosis, with or without HIV coinfection, who are either treatment-naïve (TN) or treatment-experienced (TE) to interferon (IFN) with or without ribavirin (RBV) or TE to sofosbuvir plus RBV with or without IFN. Part 1 of DORA enrolled the first cohort of subjects: adolescents 12 to < 18 years of age who were willing to swallow the adult formulation of Mavyret. Part 2 of DORA will enroll three additional cohorts: subjects age 9 to < 12 years of age (Cohort 2), 6 to < 9 years of age (Cohort 3), and 3 to < 6 years of age (Cohort 4), all of whom will receive the pediatric formulation of GLE + PIB.

Part 1 of DORA first enrolled twelve subjects into the intensive pharmacokinetic (IPK) portion to "adequately characterize the PK of a particular age group," according to the clinical study report. Subjects enrolled in the IPK portion were HIV-negative, HCV TN, and infected with an identifiable HCV genotype. Week 2 PK samples from the first six subjects were used to determine any necessary dose adjustments for GLE/PIB in the age cohort. Based on the results of the PK samples, no dose adjustments were made in Part 1 of the trial.

All 47 subjects that received the study drug in Part 1 of DORA received GLE/PIB 300 mg/120 mg. Treatment duration was defined for each subject according to HCV genotype, cirrhotic status, HCV treatment experience, and geographical location, such as is done in adults. The study drug duration was eight weeks for 44 of the 47 subjects. The study drug duration was 16 weeks for the other 3 subjects because they were HCV GT3-infected and treatment-experienced.

The trial design is considered acceptable to obtain evidence of efficacy, characterize the safety profile, and provide PK data in the adolescent population, in light of potential challenges in enrolling adolescent patients. According to the clinical review team, it is appropriate to extrapolate the efficacy observed in adults to adolescents given the high success rate observed in both patient populations.

The primary efficacy endpoint for DORA is sustained virologic response at Post-Treatment Week 12, or SVR12. SVR12 is defined as HCV RNA less than the lower limit of quantification (LLOQ) twelve weeks after the end of the treatment duration. In DORA, the LLOQ is 15 IU/mL. SVR12 is the standard primary endpoint for evaluating efficacy of HCV-indicated drugs and is considered highly predictive of long-term virologic suppression or cure.

The secondary efficacy endpoints include on-treatment virologic failure, post-treatment relapse, and HCV reinfection. On-treatment virologic failure is defined as a confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least six weeks of treatment. Post-treatment relapse is defined as HCV RNA ≥ LLOQ after the end of treatment among subjects who completed treatment and achieved HCV RNA < LLOQ at the end of treatment.

3.2.2 Statistical Methodologies

The number and percentage of subjects that achieve the primary and secondary endpoints were summarized along with a two-sided 95% confidence interval (CI). For SVR12, the 95% CI was calculated using the normal approximation to the binomial distribution, unless less than five subjects fail to achieve SVR12. In that case, the Wilson's score method was used to calculate the 95% CI. The Wilson's score method was used to calculate 95% CI for the secondary efficacy endpoints. Primary efficacy analyses were conducted in the intent-to-treat (ITT) population, defined as all randomized subjects that receive at least one dose of the study drug.

If possible, backward imputation was used for missing SVR values. If the nearest HCV RNA value after the SVR window was undetectable or unquantifiable, then it was used to input the

HCV RNA value in the SVR window. If the HCV RNA value was still missing, the value was then imputed with the HCV RNA value from a local laboratory, if possible. Otherwise, the HCV RNA value remained missing.

For SVR12, subjects with missing HCV RNA values in an analysis window were considered failures. If a subject began an alternative treatment to the test drug, then HCV RNA values measured on or after the start date of the new treatment were excluded and the subject was considered a failure.

If the HCV RNA values were missing from the central laboratory but local laboratory values were available, the local laboratory value was used to assess on-treatment virologic failure and post-treatment relapse.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 48 subjects were enrolled in the trial. However, one subject never received the study drug. As a result, 47 subjects were enrolled and treated with the study drug. All 47 subjects completed the study drug.

Most subjects enrolled and treated in Part 1 of DORA were white, female, non-Hispanic subjects from Europe and North America, with a weight of at least 45 kg. The subjects were mostly HCV GT1-infected, treatment-naïve, and were not HIV-1 infected. Part 1 of DORA did not enroll any HCV GT5- or GT6-infected subjects or subjects with cirrhosis.

Three of the 47 subjects were treatment-experienced, HCV GT3-infected subjects. Therefore, they received the study drug for 16 weeks. The three subjects were white, non-Hispanic subjects enrolled in Europe and were not HIV-1-infected. Two of the three subjects were female. In addition, two of the three subjects were age 15 at the start of the trial; the third subject was age 14. The baseline demographics and characteristics of the subjects enrolled are given below in Table 2.

Table 2: DORA (Part 1) Baseline Demographics and Characteristics

	Total (n=47)
Median age (range)	14 (12-17)
Female sex	26 (55.3%)
Race	
White	36 (76.6%)
Black	4 (8.5%)
Asian	6 (12.8%)
Other	2 (4.3%)
Hispanic ethnicity	5 (10.6%)
Geographic region	
Europe	21 (44.7%)
North America	22 (46.8%)
Japan	4 (8.5%)
Mean weight, kg (SD)	59.2 (14.1)
Weight	
≥ 45 kg	44 (93.6%)
< 45 kg	3 (6.4%)
HCV genotype	
1	37 (78.7%)
2	3 (6.4%)
3	4 (8.5%)
4	3 (6.4%)
HCV subgenotype	
1a	24 (51.1%)
1b	13 (27.7%)
2a	1 (2.1%)
2b	1 (2.1%)
2q	1 (2.1%)
3a	4 (8.5%)
4d	2 (4.3%)
4f	1 (2.1%)
HCV treatment history	
Naïve	36 (77.6%)
IFN-experienced	11 (23.4%)
Baseline HCV RNA	
< 1,000,000 IU/mL	21 (44.7%)
≥ 1,000,000 IU/mL	26 (55.3%)
Cirrhotic	0
HIV coinfection	2 (4.3%)

SD: standard deviation, HCV: Hepatitis C virus, IFN: interferon, HIV: human immunodeficiency virus
Source: reviewer created

3.2.4 Results and Conclusions

All 47 subjects achieved SVR12 (Table 3). Likewise, no subjects experienced on-treatment virologic failure, post-treatment relapse, or reinfection. Because no subjects failed to achieve SVR12, the Wilson's score method was used to calculate the 95% CI for SVR12 and no CIs were calculated for on-treatment virologic failure, post-treatment relapse, or reinfection.

Table 3: DORA (Part 1) SVR12

	MAVYRET™ 8W or 16W
SVR12	47/47 (100.0%) (Wilson 95% CI: 92.4%, 100%)
OTVF	0/47 (0%)
$Relapse_{12}$	0/47 (0%)
Other	0/47 (0%)

SVR12: sustained virologic response at Post-Treatment Week 12, OTVF: on-treatment virologic failure, $Relapse_{12}$: relapse by Post-Treatment Week 12
Source: reviewer created

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Since the overall SVR12 was 100%, all subgroups have an observed SVR12 of 100%. The 95% CIs for SVR12 rates were calculated for subgroups with a sample size of ten or more. The 95% CIs were calculated using Wilson's score method.

Due to the overall SVR12 of 100%, there were no observed differences in SVR12 that suggest the need for additional subgroup analyses.

4.1 Gender, Race, Age, and Geographic Region

Table 4 contains observed SVR12 rates for age, racial, gender, and regional subgroups.

Table 4: DORA (Part 1) SVR12 by Age, Racial, Gender, and Regional Subgroup

		MAVYRET™ 8W or 16W SVR12 (n=47)
Age (years)		
	12	6/6
	13	12/12 (100%) (75.7%, 100%)
	14	8/8
	15	9/9
	16	9/9
	17	3/3
Race		
	White	35/35 (100%)

		(90.1%, 100%)
	Black	4/4
	Asian	6/6
	Other	2/2
Gender		
	Male	21/21 (100%)
		(84.5%, 100%)
	Female	26/26 (100%)
		(87.1%, 100%)
Region		
	North America	22/22 (100%)
		(85.1%, 100%)
	Europe	21/21 (100%)
		(84.5%, 100%)
	Japan	4/4

SVR12: sustained virologic response at Post-Treatment Week 12
Source: reviewer created

4.2 Other Special/Subgroup Populations

Table 5 contains observed SVR12 rates by baseline disease characteristics, baseline weight, and study treatment duration.

Table 5: DORA (Part 1) SVR12 by Special Characteristics

		MAVYRET™ 8W or 16W SVR12 (n=47)
HCV Genotype		
	1	37/37 (100%)
		(90.5%, 100%)
	2	3/3
	3	4/4
	4	3/3
HCV Subgenotype		
	1A	24/24 (100%)
		(86.2%, 100%)
	1B	13/13 (100%)
		(77.2%, 100%)
	2A	1/1
	2B	1/1
	2Q	1/1
	3A	4/4
	4D	2/2
	4F	1/1
HCV Treatment History		
	Naïve	36/36 (100%)

	(90.4%, 100%)
IFN-experienced	11/11 (100%)
	(74.1%, 100%)
Baseline HCV RNA	
< 1,000,000 IU/mL	21/21 (100%)
	(84.5%, 100%)
≥ 1,000,000 IU/mL	26/26 (100%)
	(87.1%, 100%)
HIV coinfection	
Yes	2/2
No	45/45 (100%)
	(92.1%, 100%)
Weight (kg)	
≥ 45 kg	44/44 (100%)
	(92.0%, 100%)
< 45 kg	3/3
Study Treatment Duration	
8 weeks	44/44 (100%)
	(92.0%, 100%)
16 weeks	3/3

SVR12: sustained virologic response at Post-Treatment Week 12, HCV: Hepatitis C virus, IFN: interferon, HIV: human immunodeficiency virus
Source: reviewer created

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Part 1 of DORA enrolled 47 adolescent subjects. It is difficult to make statistical determinations about Mavyret's efficacy in subgroups of the adolescent patient population given the limited sample sizes. However, because the patient population of interest is adolescents, we recognize that the number of patients available for enrollment into the trial was likely limited. Even though the sample size is limited, the high SVR12 rate observed in Part 1 of DORA demonstrates supportive evidence of efficacy.

In addition, Part 1 of DORA did not enroll a concurrent control arm, which would have allowed an assessment of a treatment difference for Mavyret compared to an active control with minimal potential bias. However, enrolling subjects in a concurrent control arm would have further limited the number of subjects that received Mavyret, which could impact the applicant's ability to provide an appropriate safety database. Therefore, although the data is limited, we accept the use of a single-arm trial for this situation.

5.2 Collective Evidence

Part 1 of DORA assessed the steady state area under the concentration-time curve, pharmacokinetics, safety, and efficacy of Mavyret in adolescent subjects. Part 1 enrolled HCV-

infected subjects with GT 1, 2, 3, or 4, with or without HIV coinfection, who did not have cirrhosis and who were either treatment-naïve or treatment-experienced to interferon with or without sofosbuvir or ribavirin. The overall SVR12 rate (95% CI) was 100% (92.4%, 100%). No subjects experienced virologic failure.

While the sample size for Part 1 of DORA was limited, the observed efficacy in adolescent subjects appears to be strong and consistent with efficacy in adult subjects. Because the SVR12 rate was 100%, subgroup analyses did not suggest any differential treatment effects and cannot be used to identify potential baseline characteristics related to efficacy in adolescents.

5.3 Conclusions and Recommendations

Given the evidence of Mavyret's efficacy from Part 1 of DORA, it is the conclusion of the statistical review team that the evidence supports the approval of this supplemental NDA. We recommend that the indications approved for adults be extended to adolescent patients 12 years and older for the treatment of HCV.

5.4 Labeling Recommendations (as applicable)

The agency's labeling negotiations with the applicant are ongoing. The given summary represents changes recommended by the statistical review team to Section 14. The applicant accepted the recommended changes and informed the agency on March 8, 2019.

Mavyret's USPI includes a table that summarizes the clinical trials that support its effectiveness in Section 14. Figure 1 presents the addition of Part 1 of DORA to the table in the proposed label.

Figure 1: Proposed Edit to Table 10 in Section 14 of Mavyret's Label

Adolescent Subjects (12 years to less than 18 years)		
GT1-6	DORA (Part 1)	MAVYRET for 8 weeks (n=44) or 16 weeks (n=3)

DORA Part 1 added to list of clinical studies and to footnote.

Source: Annotated Draft Labeling Included in sNDA Submission (October 31, 2018), Table 10

The addition indicates GT1-6 for Part 1 of DORA. While enrollment was open to all six genotypes, Part 1 of DORA did not enroll any HCV GT5- or GT6-infected subjects. Therefore, we recommend that the addition is edited to reflect that Part 1 of DORA enrolled HCV GT1-4 infected subjects.

The applicant also submitted the following description of Part 1 of DORA presented in Figure 2 for inclusion in the labeling.

Figure 2: Description of Part 1 of DORA in the Proposed USPI

14.9 [redacted] **(12 years to less than 18 years)** [redacted] 47 subjects were enrolled in DORA (Part 1). The median age was 14 years (range: 12 to 17); 79% had HCV genotype 1, 6% had HCV genotype 2, 9% had HCV genotype 3, 6% had HCV genotype 4; 55% were female; [redacted]% were Black; 77% were HCV treatment-naïve; 23% were treatment-experienced to interferon; 4% had HIV-coinfection; none had cirrhosis; the mean weight was 59 kg (range: 32 to 109 kg). The overall SVR12 rate was 100% (47/47). [redacted]	**Annotation:** Clinical trial results from Part 1 of M16-123 (DORA) added.

Source: Annotated Draft Labeling Included in sNDA Submission (October 31, 2018), Section 14.9

The statistical review of the data found that 9%, rather than [redacted]%, of subjects were Black. We recommend changing the percentage to 9% to accurately reflect the data.

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/

THERRI A USHER
03/29/2019 04:15:24 PM

THAMBAN I VALAPPIL
03/29/2019 04:30:28 PM