Clinical and Cross-Discipline Team Leader Review

Review Completion Date	November X, 2021
From	Larissa (Lara) Stabinski, MD, MPH
Through	Yodit Belew, MD
Subject	Combined Clinical and Cross-Discipline Team Leader Review
NDA #	208261
Supplement#	S-007
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	February 19, 2021
Priority or Standard	Standard
PDUFA Goal Date	December 17, 2021
Proprietary Name	ZEPATIER™™
Non-Proprietary Name	Elbasvir (EBR) and grazoprevir (GZR)
Dosage form(s) / Strength(s)	Grazoprevir/elbasvir 100mg/50mg fixed-dose combination tablet. One tablet orally once daily.
Applicant Proposed Indication(s)/Population(s)	ZEPATIER™ is indicated for treatment of chronic HCV genotype 1 or 4 infection in adults and pediatric patients 12 years of age and older who weigh at least 30 kg. ZEPATIER™ is indicated for use with ribavirin in certain patient populations.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	ZEPATIER™ is indicated for treatment of chronic HCV genotype 1 or 4 infection in adult and pediatric patients 12 years of age and older or weighing at least 30 kg. ZEPATIER™ is indicated for use with ribavirin in certain patient populations

Benefit-Risk Summary and Assessment

Grazoprevir (GZR) is a hepatitis C virus (HCV) NS3/4A protease inhibitor and elbasvir (EBR) is an HCV NS5A inhibitor. GZR/EBR is a fixed-dose combination tablet with indication for treatment of chronic HCV genotypes (GTs) 1 or 4 infection in adults, including those with chronic kidney disease and on hemodialysis. In this application, the Sponsor proposes an expansion of the current indication to the pediatric adolescent population of children 12 years of age and older who weigh at least 30kg. The current approved dosage regimens and durations for ZEPATIER™ in Patients with Genotype 1 or 4 HCV with or without cirrhosis are as follows:

Genotype 1a: Treatment-naïve or PegIFN/RBV experienced without baseline NS5A polymorphisms (12 weeks)
Genotype 1a: Treatment-naïve or PegIFN/RBV experienced with baseline NS5Apolymorphisms (16 weeks with ribavirin)
Genotype 1b: Treatment-naïve or PegIFN/RBV experienced (12 weeks)
Genotype 1a or 1b: PegIFN/RBV/PI-experienced (12 weeks with ribavirin)
Genotype 4: Treatment-naïve (12 weeks)
Genotype 4: PegIFN/RBV-experienced (16 weeks with ribavirin)

Chronic HCV infection is a serious disease, affecting an estimated 2.4 million people in the U.S. and over 58 million people worldwide. Although often asymptomatic in early stages, if untreated, chronic HCV can lead to debilitating and life-threatening liver problems, including hepatocellular carcinoma, liver failure, and death. The current standard of care treatments for HCV infection consists of oral direct-acting antivirals (DAAs) that result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in up to 93-100% of patients. In its initial application, GZR/EBR demonstrated SVR12 ranging from 92-100% depending on the regimen, patients' HCV GT, and patients' prior treatment history. Efficacy was similar in patients with or without cirrhosis, with or without HIV coinfection, and with chronic kidney disease (CKD) with or without hemodialysis.

For this supplement, efficacy, and safety of ZEPATIER™ were evaluated in an open-label study (MK-5172-079) that evaluated pediatric subjects 12 years to less than 18 years of age who received ZEPATIER™ for 12 weeks. HCV GT1a infected subjects with one or more baseline NS5A resistance-associated substitutions (RAS) were excluded from study participation. In the MK-5172-079 study, treatment-naïve or treatment-experienced subjects 12 years to less than 18 years of age with genotype 1 or 4 chronic hepatitis, without cirrhosis, were treated with ZEPATIER™ for 12 weeks. No pediatric subjects received ribavirin. A total of 22 subjects were enrolled in the clinical trial. The median age was 13.5 years (range: 12 to 17); 50% were female; 95% were White; the weight range was 28.1 kg to 96.5 kg; 95.5% had genotype 1 and 4.5% had genotype 4; 64% were treatment-naïve, 36% were treatment-experienced; 46% had baseline HCV RNA levels greater than 800,000 IU/mL. The overall SVR12 rate was 100% (22/22). The adverse reactions observed were consistent with those observed in clinical trials of ZEPATIER™ in adults. The adverse drug reactions observed in greater than or equal to 5% of subjects receiving ZEPATIER™ were nausea (9%) and headache (14%). Approval of GZR/EBR for treatment of adolescent patients with HCV GT 1 or 4 infection or those weighing at least 30 kg is fully supported by the available evidence of efficacy and safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic hepatitis C viral infection (HCV infection) causes inflammation of the liver that can lead to long-term health problems or death. If left untreated, HCV infection can lead to cirrhosis, hepatocellular carcinoma, liver failure, and death. HCV infection is a leading cause of chronic liver disease in the U.S. • HCV infection is a global health problem, with over 58 million individuals chronically infected worldwide. Although the prevalence of chronic HCV is lower in children than in adults, an estimated 3.26 million children worldwide have active HCV infection. • In the US, from 2011 to 2018, the estimated acute infections per year have tripled, particularly among youth and young adults. This increase is associated with the opioid crisis and intravenous drug use (IVDU). • There are at least six distinct HCV genotypes (GTs). Most common among U.S. patients is GT 1 (72%). GT 4 represents about 6% of infections. HCV infection is typically asymptomatic in its early stages.	If untreated, chronic HCV infection is a life-threatening condition, one that affects a large population. Patients infected in utero or as children or adolescents can experience symptoms that are severe and debilitating later in life and are at risk of transmitting HCV to others. HCV infection in adolescents is a significant and growing public health concern.
Current Treatment Options	• HCV therapy for adolescents has shifted from interferon-based regimens, to shorter duration, once daily oral pills that are highly effective, curative and with fewer side effects. • Therapy is now indicated for all adolescents with hepatitis C virus infection, regardless of stage of liver disease, recent IVDU, or coinfection with HIV.	Although ZEPATIER™ is not the shortest available regimen, and in some cases requires concomitant use of ribavirin, the treatment armamentarium for adolescents would benefit from additional therapeutic options that are well tolerated and equally efficacious, particularly for common GT 1 infections.
Benefit	• The efficacy of GZR/EBR was previously established in five clinical trials (three Phase 3, one Phase 2/3, and one Phase 2), with a total of 1155 HCV patients across all trials. • The primary efficacy endpoint was SVR12, or virologic cure. SVR12 results overall ranged from 92-100% for the adult populations studied. • For children, the efficacy of ZEPATIER™ was evaluated in an open-label study (MK-5172-079) that included 22 adolescent pediatric subjects in Cohort 1, 12 years to less than 18 years of age who received ZEPATIER™	Five clinical trials provide substantial evidence of effectiveness of GZR/EBR in genotype 1 and 4 HCV infection. The effectiveness in the adolescent study was high and similar to that in the adult population. Extending this indication to children weighing

	for 12 weeks, weight ranging from 28.1 kg to 96.5 kg. (Median body weight in the Mini (PK) cohort was 56 kg, range 42 to 97 kg.) The overall SVR12 rate in adolescents was 100% (22/22). • Included in MK-5172-079, was also a Cohort 2 (aged 7 to <12 years, median body weight in the Mini (PK) cohort 33 kg, range 22 to 48 kg), who were treated with were treated with EBR/GZR (30 mg/60 mg) pediatric granules. The overall SVR12 rate in this cohort was also 100% (17/17).	at least 30 kg, would further improve access to children and adolescent HCV patients, who may be underweight, given this chronic disease. Efficacy in this weigh band was similarly high to that of adolescents, even at a lower dose.
Risk	• The safety database for adults GZR/EBR included the five aforementioned clinical trials and was considered adequate. • Rare, late ALT elevation without clinical sequala was safety issue identified in the initial review of adult subjects. This drug also has a warning for risk of hepatic decompensation/failure in those with advanced liver disease. In adults, fatigue, headache, nausea, and asthenia were the most common adverse events (AEs) reported across trials and occurred at a similar rate with placebo. • The adolescent cohort was relatively small (n=22). Adverse reactions observed in adolescents were consistent with those observed in clinical trials of ZEPATIER™ in adults, although there was no pattern of increased ALT observed. The adverse drug reactions observed in greater than or equal to 5% of subjects receiving ZEPATIER™ were nausea (9%) and headache (14%). There was no negative impact on growth or development. • The MK-5172-079 study included treatment-naïve or treatment-experienced subjects 1 with genotype 1 or 4 chronic hepatitis C, without cirrhosis. No pediatric subjects received ribavirin. HCV GT1a infected subjects with one or more baseline NS5A RAS were excluded from study participation. • Adult subjects treated with GZR/EBR and RBV had notably higher rates of most AEs compared to GZR/EBR without RBV. All were common and well-known RBV-related adverse reactions. Additionally, RBV-treated subjects had a higher rate of discontinuation due to psychiatric AEs. • Pediatric EBR exposures at the 50 mg dose were comparable to the reference adult exposure. The GZR exposures for the adolescent cohort were low	Hepatic safety issues with GZR/EBR at the proposed marketed dosages are well characterized. A pattern of ALT elevation was not observed, although the cohort size may have been too small to detect this type of laboratory trend and none of the subjects were cirrhotic. Otherwise, adverse drug reactions were similar in children and adults and would not be expected to vary across adolescent sub-populations not included in MK-5172-079. The safety issues with RBV are well known and are not exacerbated by GZR/EBR. Although not studied with RBV in adolescents, GZR/EBR with or without RBV demonstrated an overall favorable safety profile. The adolescent cohort already received the maximum approved dose of GZR (100 mg, provided in the adult FDC formulation. Further, in the Mini Age Cohort 2 (aged 7 to

	compared to the adult value, however, the 95% CI included the reference adult exposure.	<12 years, median body weight 33 kg, range 22 to 48 kg), both EBR exposures at 30 mg and GZR exposures at 60 mg were comparable to the reference adult exposure (with an SVR 12 of 100%) even at this lower dose. Safety at this weight was comparable to that in the adolescent and adult populations.
Risk Management	• Although the adolescent cohort was small and did not include cirrhotic subjects, subjects requiring RBV or treatment for 16 weeks or certain baseline mutations, the indications was extended for all subpopulations pertaining to adolescents to allow practitioners to choose the best treatment option for their patient.	Hepatic and other safety issues are well documented and positioned in the label. The subpopulations are studied in adults and are well described in the label.

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 Elbasvir (EBR) and grazoprevir (GZR) use in pediatric patients 12 years of age and older with chronic Hepatitis C Virus (HCV) genotype (GT) 1 or 4 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).

HCV infection is a global health problem, with over 58 million individuals chronically infected worldwide. Although the prevalence of chronic HCV is lower in children than in adults, an estimated 3.26 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. From 2011 to 2018, the estimated acute infections per year have tripled, particularly among youth and young adults. This increase is associated with the opioid crisis and intravenous drug use (IVDU).[2] There are 8 identified HCV genotypes (GT), with GT 1 being the most prevalent worldwide. HCV GT4 is found in higher frequency in parts of Africa and the Middle East and immigrants from these regions.

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.

Current standard-of-care utilizes multiple DAAs in combination (often fixed-dose combination regimens) to maximize SVR while limiting viral resistance and side effects. 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 and children.

Supplemental NDA application S-7 supports approval of EBR/GZR for treatment of chronic HCV GT 1 or 4 infection without cirrhosis or with compensated cirrhosis in pediatric patients 12

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[1] Global prevalence of hepatitis C virus in children in 2018: a modelling study. Lancet Gastroenterol Hepatol. 2020 Apr;5(4):374-392. doi: 10.1016/S2468-1253(19)30385-1. Epub 2020 Jan 16.
[2] Adolescent Hepatitis C: Prevalence, Impact, and Management Challenges. Adolesc Health Med Ther. 2021; 12: 45–53.

years of age and older. The data discussed are primarily derived from Cohort 1 of study MK-5172-079 entitled, "A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/ Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection". Cohort 1 includes adolescent subjects ≥ 12 years of age treated with the adult regimen. If approved, EBR/GZR would make another DAA regimen available for adolescent children with chronic HCV infection and GT 1 or 4 infection.

2. Regulatory Background

ZEPATIER™ is a fixed-dose combination product containing elbasvir (EBR), an HCV NS5A inhibitor, and grazoprevir (GZR), an HCV NS3/4A protease inhibitor. ZEPATIER™ was initially approved in 2016 and is indicated for treatment of chronic HCV genotype 1 or 4 infection in adults. ZEPATIER™ is indicated for use with ribavirin in certain patient populations

The duration of treatment with EBR/GZR in adults was based on a combination of factors including prior treatment experience and HCV genotype, as detailed in **Table 1**.

Table 1. Dosage Regimens and Durations for ZEPATIER™ in Patients with Genotype 1 or 4 HCV with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†	ZEPATIER™	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	ZEPATIER™ + ribavirin	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*	ZEPATIER™	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced‡	ZEPATIER™ + ribavirin	12 weeks
Genotype 4: Treatment-naïve	ZEPATIER™	12 weeks
Genotype 4: PegIFN/RBV-experienced*	ZEPATIER™ + ribavirin	16 weeks

*Peginterferon alfa + ribavirin.
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor.

Source: ZEPATIER™ USPI

To better understand the potential use of ZEPATIER™ in pediatric patients, PREA PMR 3008-1 was issued with the original NDA approval on January 28, 2016 and requested the following: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of elbasvir and grazoprevir in pediatric subjects 3 to 17 years of age with chronic hepatitis C infection.

Subsequently, as the landscape of HCV oral therapy evolved and additional pediatric regimens were approved, the Sponsor sought a release from PREA PMR 3008-1. The Sponsor was granted a release for patients under the age of 12, on April 13, 2020, for the following reasons: Elbasvir/grazoprevir fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients 3 to less than 12 years of age and is unlikely to be used in a substantial number of pediatric patients 3 to less than 12 years of age.

PREA PMR 3008-1 was replaced by PREA PMR 3818-1: Conduct a study to evaluate the pharmacokinetics, safety and treatment response using sustained virologic response of elbasvir and grazoprevir in pediatric subjects 12 to 17 years of age with chronic hepatitis C infection, with a study completion target date of 7/2020 and final report submission of 7/2021.

Study MK-5172-079 entitled, “A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/ Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection”, was developed in accordance with the initial PREA PMR. The clinical study report has been submitted in part as a response to the PREA PMR 3818-1. Cohort 1 of this study includes adolescent subjects ≥ 12 years of age treated with the adult regimen of ZEPATIER™ and is the focus of this review. Safety and efficacy data were also submitted for children from 3 to <12 years of age in the CSR, however, an indication was not sought for this population, and there is not a plan to develop EBR/GZR for this population. For this reason, safety, and efficacy data for children 3 to <12 years of age are presented and reviewed in this document, when relevant, only in support of the adolescent indication.

3. CMC/Device

For a description of the product quality assessment, please refer to the original ZEPATIER™ NDA 208261 review. No new product quality information is included with S-7 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 ZEPATIER™ NDA.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology data for EBR and GZR were extensively reviewed in the original EBR/GZR NDA review. No new nonclinical pharmacology/toxicology information is included with S-7.

5. Clinical Pharmacology/Biopharmaceutics

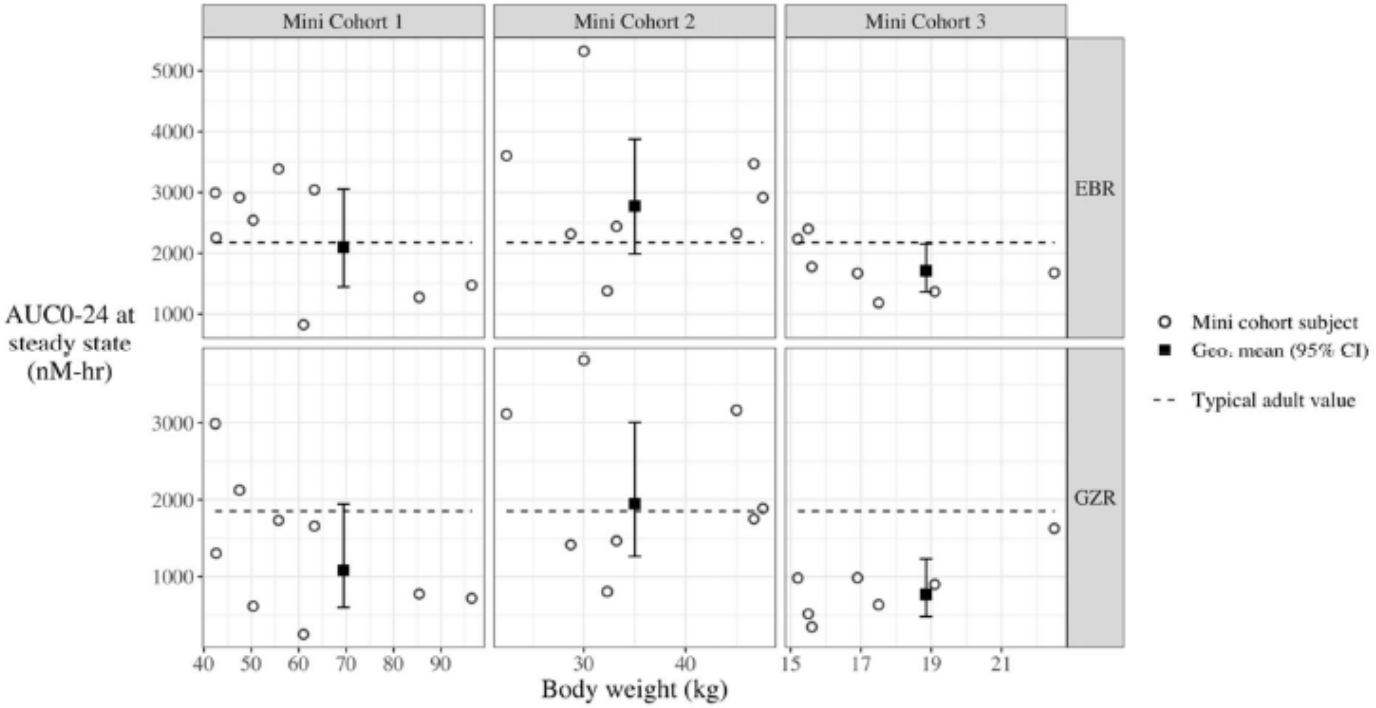
The basis of approval of ZEPATIER™ in adolescent subjects is extrapolation of efficacy from adult subjects by matching systemic exposures of EBR and GZR between adults and adolescents with HCV infection.

Please see the Clinical Pharmacology review by Dr. Yang Zhao and colleagues for complete details of the clinical pharmacology and pharmacometrics evaluation. In short, data from study demonstrate that the mean systemic exposures of EBR and GZR are comparable between adults and adolescent subjects when the adult dosing regimen of ZEPATIER™ is administered to adolescent subjects.

The steady-state Week 4 plasma AUC0-24 in each Mini Age Cohort was compared to the reference adult EBR and GZR steady-state exposure for the approved 50/100 mg QD dose to confirm the dose of EBR and GZR to be administered in the corresponding Expanded Age Cohort. A graphical comparison of the exposures between the adult reference and in Mini Age Cohort 1 is provided summarized below and depicted in **Figure 1.**

Mini Age Cohort 1 (aged 12 to <18 years, median body weight 56 kg, range 42 to 97 kg):
Pediatric EBR exposures at the 50 mg dose were comparable to the reference adult exposure. While GZR exposures for this cohort were low compared to the adult value, the 95% CI included the reference adult exposure. Furthermore, this cohort already received the maximum approved dose of GZR (100 mg, provided in the adult FDC formulation. Of note, within the same study the Mini Age Cohort 2 (aged 7 to <12 years, median body weight 33 kg, range 22 to 48 kg), both EBR exposures at 30 mg and GZR exposures at 60 mg were comparable to the reference adult exposure (with an SVR 12 of 100%) even at this lower dose.

Figure 1. Plasma AUC0-24 of EBR (MK-8742) and GZR (MK-5172) at Steady State (Week 4; Day 28) for Mini Age Cohorts Compared to Reference Adult Steady State Values



AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; CI=confidence interval; EBR=elbasvir; GZR=grazoprevir.
Adult steady state values referenced in [Table 9-4].
Source: [P079V01MK5172: adam-adpp]

6. Clinical Microbiology

The efficacy supplement is considered approvable from a Clinical Virology perspective based on the high efficacy of EBR/GZR observed in adolescent subjects in Cohort 1 of MK-5172-079 (SVR12=22/22 [100%]). Nine of the 22 participants in Age Cohort 1 had an NS3-associated polymorphism. the single participant with GT4d infection from Age Cohort 1 had an NS3 RAS, S122N, at baseline. There was no impact of baseline NS3 RAS on efficacy; all participants achieved SVR12. No changes were proposed for Section 12.4 Microbiology of the ZEPATIER™ 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, and certain subgroups included in the approved indication were not represented (e.g., patients with cirrhosis, those with HCV genotype 1a with baseline NS5A polymorphisms and genotype 4 with treatment experience). Nevertheless, the efficacy and resistance characteristics of EBR/GZR are anticipated to be similar in adults and children, provided drug exposures are comparable. The relatively limited data from Cohort 1 of MK-5172-079 are sufficient to confirm EBR/GZR is reasonably effective in the adolescent population.

7. Clinical/Statistical - Efficacy

Efficacy Summary
As discussed in Section 5, pharmacokinetic data provide data to support approval of the currently marketed EBR/GZR formulation for adolescent patients. This section summarizes the SVR12 data for Cohort 1 of MK-5172-079, which provide supportive evidence of efficacy.

Extrapolation of efficacy for HCV DAAs such as EBR/GZR 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). DAV 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[3].

The submitted data demonstrate that administration of EBR/GZR 50mg/100mg (given as one 50 mg/100mg tablets once daily) in pediatric participants ages ≥12 to <18 years was efficacious. One hundred percent of participants enrolled in MK-5172-079 achieved SVR 12. No participants experienced virologic breakthrough or viral relapse. Further, EBR/GZR pharmacokinetics and previous trials in adults have demonstrated that equivalent EBR/GZR exposure is efficacious in adults with chronic HCV GT 1 or 4 infection with and without 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 and data verification included in this review were performed by the clinical reviewer using JReview software. Tables were not replicated for this review. However, the data and tables included in this document were verified. Data review is focused on the adolescent population or Cohort 1 of Study MK-5172-079. Of note, the Sponsor

[3] AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/search/benefits%20of%20treatment. Accessed October 10, 2021

did not submit a 4 month safety report as all safety data was submitted and was reviewed with this application.

7.2 Indication

S-7 requests approval of EBR/GZR for treatment of chronic HCV GT 1 and 4 without cirrhosis or with compensated cirrhosis in pediatric patients 12 years of age and older.

7.3 Study Design

Study MK-5172-079 was a nonrandomized, single arm, multiple cohort, multisite, open-label Phase 2b study of EBR/GZR in non-cirrhotic pediatric participants, 3 to <18 years of age, with CHC GT1 or GT4 infection; all participants received EBR/GZR, without RBV, for 12 weeks with 24 weeks of follow-up. Participants were enrolled into 3 Age Cohorts (1, 2, and 3), each consisting of a Mini Age Cohort (first 7 participants enrolled) and an Expanded Age Cohort.

Cohort 1: Age 12 to <18 years. N=22 participants across Mini and Expanded cohorts. EBR/GZR was administered orally once-daily, as an FDC tablet (50 mg/100 mg).

Cohort 2 & 3: Age 3 to <12 years. N=35 participants. EBR/GZR was administered orally once daily, as granules.

The primary objective of MK-5172-079 was to evaluate the steady-state EBR and GZR PK in children and adolescents by age. Secondary objective were safety and efficacy, which was assessed as SVR12. Viral resistance and SVR24 were included as exploratory efficacy endpoints.

7.4 Demographics and Clinical Characteristics

Twenty-two adolescent participants were enrolled in Cohort 1. Select characteristics of the trial population are summarized in **Table 2**.

Table 2. Subject Characteristics

	Age Cohort 1 (12 to <18 years): Mini and Expanded	
	n	(%)
Subjects in population	22	
Gender		
Male	11	(50.0)
Female	11	(50.0)
Age (Years)		
3 to <7 years	0	(0.0)
7 to <12 years	0	(0.0)
12 to <18 years	22	(100.0)
Mean	14.1	
SD	1.9	
Median	13.5	
Range	12 to 17	
Race		
Multiple	1	(4.5)
Native Hawaiian Or Other Pacific Islander, White	1	(4.5)
White	21	(95.5)
Ethnicity		
Hispanic Or Latino	3	(13.6)
Not Hispanic Or Latino	19	(86.4)
Not Reported	0	(0.0)
HCV Genotype		
1a	16	(72.7)
1b	5	(22.7)
4a	0	(0.0)
4d	1	(4.5)
Prior Treatment History		
Treatment Naïve	14	(63.6)
PR Treatment Experienced	8	(36.4)
Baseline HCV RNA (IU/mL)		
Subjects with data	22	
Mean	1406305	
SD	2080769.6	
Median	749334	
Range	78579 to 9428091	

Source: Table 2.7.4-hepcadol: 2 (CSR)

The majority of participants were white (95.5%), and not Hispanic or Latino. The cohort was equally divided by gender. All participants were non-cirrhotic and had CHC GT1a (72.7%), GT1b (22.7%), or GT4d (4.5%) infection. Notably, of the 22 participants in this cohort only one had genotype 4 infection. Eight (36.4%) participants were treatment-experienced, all had been previously treated with IFN and RBV. The weight range was 28.1 kg to 96.5 kg. (The median body weight in PK Mini Age Cohort 1 was 56 kg, range 42 to 97 kg.)

7.5 Participant Disposition

All participants in Age Cohort 1 (Mini and Expanded) were treated with the EBR/GZR (50 mg/100 mg) FDC tablet. Twenty-two participants (100%) in Cohort 1 completed study treatment and all achieved SVR12. This was the same across all three of the study cohorts; all 57 subjects allocated across 14 study sites completed the study regimen as per protocol and achieved SVR12. Twenty-one participants were not allocated; 20 were screen failures and 1 had consent withdrawn. The study was not blinded and therefore premature unblinding could not occur by design.

While no participants were excluded from the study for protocol violations, there were two subjects in Cohort 1 considered to have important protocol deviations. One subject had no (initial) documented informed child assent (documented informed consent from the legally acceptable representative was obtained prior to entry). One participant in Age Cohort 1 also entered the study with a history of gastroduodenal surgery, a condition specified as exclusionary in the protocol. The reviewer agrees 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, although measured drug exposures for the single subject with prior gastroduodenal surgery could have been affected (although this subject achieved SVR 12).

7.6 Analysis of Primary Efficacy Endpoint (Secondary Study Endpoint)

The primary efficacy endpoint of the trial was SVR 12 weeks after stopping study treatment (SVR12) for all enrolled and treated participants, including adolescents. One hundred percent of enrolled participants achieved SVR12 and no participants experienced on-treatment virologic failure or relapse (**Table 3**). No participants were lost to follow-up.

Table 3. SVR 12 All Pediatric Cohorts

Cohort	N	n (%)	95% Confidence Interval[†]
Age Cohort 1 (12 to <18 years): Mini and Expanded	22	22 (100.0)	(84.6, 100.0)
Age Cohort 2 (7 to <12 years): Mini and Expanded	17	17 (100.0)	(80.5, 100.0)
Age Cohort 3 (3 to <7 years): Mini	7	7 (100.0)	(59.0, 100.0)
Age Cohort 3 (3 to <7 years): Expanded	11	11 (100.0)	(71.5, 100.0)
Total	57	57 (100.0)	(93.7, 100.0)

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects who achieved undetectable (TND) or unquantifiable (TD(u)) HCV RNA and the percentage calculated as (n/N)*100.
LLoQ is 15 IU/mL.

Source: [P079V01MK5172: adam-adsl; adhcvrna]

7.7 Other Efficacy Analysis
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. Palatability Score
The majority (64%) of participants in Age Cohort 1 reported the taste of the EBR/GZR FDC tablet as “Neither Good Nor Bad” at TW4 and TW8 and did not report a problem taking the dose. Thirty-three percent rated the taste as “Very Good or Good” and 14% stated it was “Bad or Very Bad” in taste. One participant had problems taking the dose or spitting out medication. However, all adolescents completed the treatment regimen and no adolescents experienced gagging.

8. Safety

Safety Summary
Results from MK-5172-079 demonstrate that EBR/GZR was safe and well-tolerated in adolescents. Overall, the adverse events observed were similar to those observed in adult clinical trials. Subgroup assessment was very limited given the small sample size overall and in demographic sub-groups.

8.1. Methods

All twenty-two of the fifty-seven enrolled adolescent participants (Cohort 1) in trial MK-5172-079 were included in the safety analysis of EBR/GZR in pediatric participants ages ≥ 12 to < 18 years.

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

AEs are coded using MedDRA 22.1. The sNDA S-7 submission includes the AE dictionary files that consist of all verbatim and the preferred/dictionary-derived terms. The Sponsor'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. Data in the presented safety tables were verified; however, for the most part tables were not recreated. Although the focus of this review was on the adolescent population, data from the other pediatric cohorts is selectively included for comparison. As stated above, the Sponsor did not submit a 4-month safety report as all safety data was submitted and was reviewed with this application.

8.2 Adequacy of Safety Assessments

The safety monitoring plan implemented in trial MK-5172-079 was adequate. Study visits in the Treatment Phase occurred on Day 1 and at the end of weeks 1, 2, 4, 8 and 12. Follow-up visits occurred 4, 8,12,16 and 24 weeks after treatment. Each visit included: an assessment of AEs, medication adherence (on treatment), and concomitant medications. Physical exams with vital signs, height and weight and safety and virology laboratory studies were done on Day 1 and weeks 4, 8 and 12 on treatment and follow up week 12 and 24.

8.3 Major Safety Results

For the adolescent cohort and across the entire study there were no drug related serious adverse reactions. No deaths occurred during the study. No AEs led to premature discontinuation. (**See Table 4 below**). One participant in adolescent Cohort 1 experienced a serious adverse event (SAE) of hand fracture, and one subject in Cohort 3 experienced a SAE of dyspepsia for10 hours, both events were considered not to be drug related by the investigator.

Table 4. Safety Results Summary All Pediatric Cohorts

	Age Cohort 1 (12 to <18 years): Mini and Expanded		Age Cohort 2 (7 to <12 years): Mini and Expanded		Age Cohort 3 (3 to <7 years): Mini		Age Cohort 3 (3 to <7 years): Expanded		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	22		17		7		11		57	
with one or more adverse events	18	(81.8)	13	(76.5)	6	(85.7)	9	(81.8)	46	(80.7)
with no adverse event	4	(18.2)	4	(23.5)	1	(14.3)	2	(18.2)	11	(19.3)
with drug-related† adverse events	6	(27.3)	3	(17.6)	1	(14.3)	0	(0.0)	10	(17.5)
with serious adverse events	1	(4.5)	0	(0.0)	0	(0.0)	1	(9.1)	2	(3.5)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.

Source: [P079V02MK5172: adam-adsl; adae]

8.4 Dropouts and Discontinuations.

No participants discontinued study drug with study drug due to an AE. All participants who started treatment went on to complete therapy. 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 MK-5172-079. Across the entire study including Cohort 1, the majority of AES were mild in intensity and no subject experienced an event of severe intensity. Overall, approximately 75% of all participants and 73% of adolescent participants experienced an adverse event and approximately 27% of adolescents and 18% of the overall pediatric population experienced an event that was determined to be related by the investigator (ADR). The six adolescents in Cohort 1 with ADRs experienced: Headache (3 subjects) Nausea (2 subjects) and one subject each Arthralgia, Asthenia, Chills, Fatigue, Flatulence, and Somnolence. All were considered mild. (See Table 5 below).

Table 5: Adverse Drug Reactions (ADRs)

	Age Cohort 1 (12 to <18 years): Mini and Expanded		Age Cohort 2 (7 to <12 years): Mini and Expanded		Age Cohort 3 (3 to <7 years): Mini		Age Cohort 3 (3 to <7 years): Expanded		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	22		17		7		11		57	
with one or more drug-related adverse events	6	(27.3)	3	(17.6)	1	(14.3)	0	(0.0)	10	(17.5)
with no drug-related adverse events	16	(72.7)	14	(82.4)	6	(85.7)	11	(100.0)	47	(82.5)
Gastrointestinal disorders	**3**	**(13.6)**	**1**	**(5.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(7.0)**
Abdominal pain upper	0	(0.0)	1	(5.9)	0	(0.0)	0	(0.0)	1	(1.8)
Diarrhoea	0	(0.0)	1	(5.9)	0	(0.0)	0	(0.0)	1	(1.8)
Flatulence	1	(4.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)
Nausea	2	(9.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.5)
General disorders and administration site conditions	**2**	**(9.1)**	**2**	**(11.8)**	**1**	**(14.3)**	**0**	**(0.0)**	**5**	**(8.8)**
Asthenia	1	(4.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)
Chills	1	(4.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)
Fatigue	1	(4.5)	2	(11.8)	1	(14.3)	0	(0.0)	4	(7.0)
Investigations	**0**	**(0.0)**	**1**	**(5.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.8)**
Alanine aminotransferase increased	0	(0.0)	1	(5.9)	0	(0.0)	0	(0.0)	1	(1.8)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(5.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.8)**
Decreased appetite	0	(0.0)	1	(5.9)	0	(0.0)	0	(0.0)	1	(1.8)
Musculoskeletal and connective tissue disorders	**1**	**(4.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.8)**
Arthralgia	1	(4.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)
Nervous system disorders	**3**	**(13.6)**	**1**	**(5.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(7.0)**
Headache	3	(13.6)	1	(5.9)	0	(0.0)	0	(0.0)	4	(7.0)
Somnolence	1	(4.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(14.3)**	**0**	**(0.0)**	**1**	**(1.8)**
Restlessness	0	(0.0)	0	(0.0)	1	(14.3)	0	(0.0)	1	(1.8)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(5.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.8)**
Proteinuria	0	(0.0)	1	(5.9)	0	(0.0)	0	(0.0)	1	(1.8)

Every subject is counted a single time for each applicable row and column.

Source: [P079V01MK5172: adam-adsl; adae]

Compared to adult safety data from the original ZEPATIER™ NDA clinical review of subjects treated for 12 weeks (C-EDGE, N=316), adolescents experienced adverse drug reactions of the similar nature and similar frequency. Adults (C-EDGE) experienced: **Fatigue** 11%, **Headache** 10%, and **Nausea** 5%, as common ADRs. Adolescents in MK-5172-079, experienced: **Headache** 14%, **Nausea** 9%, **Fatigue** 5%, the latter by rounding. The similarity is especially evident if one considers that with small population sizes proportions can be skewed by single events. Similarly, overall, across the pediatric cohorts, adverse drug reactions of greater than equal to 5% were **Fatigue** (7%) and **Headache** (7%). In the original review of adult data in C-EDGE these events were similar in frequency to placebo; however, placebo comparison was not available for this pediatric study.

8.6 Laboratory Findings

Laboratory evaluations were assigned toxicity grades according to a severity scale established in the original trial protocol. There were no clinically significant trends in laboratory evaluations. In Age Cohort one, mean reductions from baseline in ALT and AST and small mean changes (increases and decreases), in bilirubin, not associated with clinical events and considered not clinically meaningful, were observed throughout the treatment and follow-up periods. A single

non-cirrhotic participant in Age Cohort 2 had an increased ALT of 218 IU/L on Day 29, L (Grade 3: 6.2 × ULN of 35 IU/L and 3.6 × baseline value of 61 IU/L) which met ECI criteria per protocol and was considered by the investigator to be related to study intervention. This participant also experienced decreased appetite, fatigue, diarrhea, and upper abdominal pain. No action was taken, the subject remained on the study drug and the ALT elevation resolved approximately 2 weeks after onset. In summary, no new safety concerns related to liver toxicity in the adolescent or pediatric population were identified.

8.6.1 Events of Special Interest
One participant in the adolescent cohort experienced an overdose, as well as 2 across the study. No overdoses resulted in an AE and all were either a result of a parent accidently giving an extra dose (2) or redosing after vomiting (1).

8.7 Product-Specific Primary Safety Concerns
The Warnings and Precautions Section of the label contains a risk of Hepatitis B Virus reactivation, ALT elevations and risks associated with ribavirin combination treatment. There is also a warning about Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease. No subjects were coinfected with HBV nor treated with ribavirin. No adolescent subjects experienced significant ALT elevations. No subject met criteria for Hy's Law. A single subject I Cohort 2 experienced transient ALT elevation, as discussed above, which met event of clinical interest (ECI) criteria. No additional product-specific primary safety concerns were studied or identified in this pediatric supplement.

8.8 Growth and Development in Adolescents
Study MK-5172-079 was of short duration and not powered to detect meaningful differences in growth parameters. Further growth parameters are expected to be highly variable in the adolescent age group. From baseline to Treatment Week 12 (TW12) and Follow Up Week 12 (FW12), small changes in height, weight, and BMI Z-scores occurred in the adolescent cohort consistent with normal pediatric development during and following therapy: height (TW 12: 0.01, FW 12: -0.01), weight (TW12: 0.04, FW 12;0.08), and BMI (TW 12: 0.04, FW 12:0.07).

8.9 Race, Ethnicity, and Gender
Protocol MK-5172-079 was not powered to detect differences between these individual populations. However, race, ethnicity, and gender did not appear to influence the frequency or severity of adverse drug reactions.

9. Subpopulations

Baseline characteristics (including age, gender, race, BMI, and measures of renal or hepatic function) were studied to determine their effects on the PK of EBR/GZR in the adult development program. With the exception of moderate and severe hepatic insufficiency (Child-Pugh B and C), none of these factors were found to cause clinically significant differences in adults. There was no identified exposure-safety relationship in adult participants for EBR. For GZR, a >2% risk of ALT/AST elevation was found for adult participants at exposures above the

clinical upper bound (5-fold higher than the reference exposure) (see original application and original clinical NDA review). Analysis of the relationship between exposure and weight was performed for study MK-5172-079, demonstrating that exposures for both EBR and GZR are expected to remain below the clinical upper bound for adolescents weighing ≥30 kg.

Conversely, as discussed above, pediatric EBR exposures at the 50 mg dose were comparable to the reference adult exposure. While GZR exposures for Cohort 1were low compared to the adult value, the 95% CI included the reference adult exposure and SVR 12 was achieved in all subjects (100%) in the adolescent population. Furthermore, this cohort already received the maximum approved dose of GZR (100 mg, provided in the adult FDC formulation). Additionally, in Cohort 2, (aged 7 to <12 years, median body weight 33 kg, range 22 to 48 kg) both EBR exposures at 30 mg and GZR exposures at 60 mg were comparable to the reference adult exposure (with an SVR 12 of 100%) even at this lower dose.

Further, the adult EBR/GZR development program included clinical trials that included several subpopulations of patients including those with cirrhosis, HIV-1/HCV coinfection, advanced kidney disease and treatment experienced subjects. Adult clinical trial results demonstrate a favorable risk/benefit assessment of EBR/GZR in these populations and provide supportive rational for expanding the indication for use in adolescents.

10. Advisory Committee Meeting

Not applicable.

11. Pediatrics

As discussed above in Section 2, one PREA Post-marketing Requirement (PMR) for pediatric patients was issued in the initial approval letter for the EBR/GZR NDA.

PREA PMR 3008-1 was issued with the original NDA approval on January 28, 2016 and requested the following:

Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of elbasvir and grazoprevir in pediatric subjects 3 to 17 years of age with chronic hepatitis C infection.

Subsequently as the landscape of HCV oral therapy changed additional pediatric regimens were approved, the Sponsor sought a release from PREA PMR 3008-1. The Sponsor was granted a release for patients under the age of 12, on April 13, 2020 for the following reasons:

Elbasvir/grazoprevir fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients 3 to less than 12 years of age and is unlikely to be used in a substantial number of pediatric patients 3 to less than 12 years of age.

PREA PMR 3008-1 was replaced by PREA PMR 3818-1:

Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response (SVR)) of elbasvir and grazoprevir in pediatric subjects 12 to 17 years of age with chronic hepatitis C infection, with a study completion target date of 7/2020 and final report submission of 7/2021.

This application in part in response to PMR 3818-1. PMR 3818-1 is considered fulfilled with the approval of this Supplement. The Sponsor is claiming (b) (4) Merck also requested a waiver to submit a 4-month safety update report on the basis that there are no ongoing or planned studies (or study extensions) with ZEPATIER™ and that all the safety data from the studies supporting this sNDA have been submitted in the application. This waiver was granted.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Based on the totality of the data presented and input from the review disciplines, the clinical review team recommends approval of EBR/GZR at the adult dose (50mg/100mg FDC tablet, administered once daily) for the treatment of pediatric patients 12 years of age and older or weighting at least 30 kg with HCV GT 1 or 4.

Risk Benefit Assessment
The overall risk benefit assessment is favorable for EBR/GZR. Efficacy and safety data presented in this sNDA do not alter the risk-benefit assessments made during the original NDA and supplemental reviews of EBR/GZR. One hundred percent of participants enrolled in 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 or those weighing ≥ 30 kg with HCV genotype 1 or 4 infection. (See also risk benefit analysis template above).

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 MK-5172-079, the Agency and Sponsor are engaged in finalizing discussions over labeling revisions. These currently include:

- 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.
- Trial description in 14.6
- Updates to the corresponding sections of patient labeling

14. Other Relevant Regulatory Issues

Clinical Investigator Financial Disclosure Review Template.
Application Number: 208261 S-7

Submission Date(s): February 19, 2021

Applicant: Merck Sharp & Dohme Corp.

Product: ZEPATIER™

Reviewer: Larissa (Lara) Stabinski, MD

Date of Review: October 10, 2021

Covered Clinical Trial (Name and/or Number): MK-5172-079

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **58**		
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): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of 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: 1		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	**Yes** ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	**Yes** ☒ (section 1.3.4)	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	**N/A** ☒	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*. Only one of the investigators had reportable financial disclosures or certifications of due diligence and a description was provided as to how the study design minimized bias.

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/

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