Combined Clinical, Clinical Virology, Statistics, Cross-Discipline Team Leader, and Division Director Summary Review

Date	June 6, 2025
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Subject	Combined Clinical, Clinical Virology, Statistics, and Cross-Discipline Team Leader, and Division Director Summary Review
NDA/BLA # and Supplement#	NDA 209394 Supplement-19 NDA 215110 Supplement-05
Applicant	AbbVie Inc.
Date of Submission	December 20, 2024
Priority or Standard	Priority
PDUFA Goal Date	June 20, 2025
Proprietary Name	MAVYRET
Established or Proper Name	Glecaprevir/pibrentasvir
Dosage Form(s)	Oral tablet/oral pellet fixed dose combination ▪ Tablets: 100 mg glecaprevir and 40 mg of pibrentasvir ▪ Pellets: 50 mg glecaprevir and 20 mg pibrentasvir in each packet
Applicant Proposed Indication(s)/Population(s)	Acute hepatitis C virus (HCV) infection
Applicant Proposed Dosing Regimen(s)	Adults and pediatric patients ages 12 and older: Glecaprevir 300mg and pibrentasvir 120 mg total daily dose taken orally once daily for 8 weeks Pediatric patients 3 to less than 12 years of age: Weight based dosing once daily for 8 weeks
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	MAVYRET is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 3 years and older with **acute or** chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).

1. Executive Summary

1.1 Regulatory Action

The supplemental new drug applications 209394/S-19 (oral tablet) and 215110/S-05 (oral pellet formulation) were submitted by AbbVie to expand the MAYVRET indication to include treatment of acute HCV infection. MAVYRET was approved for the treatment of chronic HCV infection on August 3, 2017. These supplements were reviewed by a multidisciplinary team. The review team recommends approval of MAVYRET for the treatment of acute HCV infection.

The Applicant submitted data generated from one adequately designed Phase 3 trial, M20-350, that provided substantial evidence of effectiveness for the proposed indication. Safety data from M20-350 demonstrate that MAVYRET was well tolerated and the observed safety profile in participants with acute HCV infection was similar to the well-characterized safety and tolerability profile across multiple subpopulations in patients with chronic HCV infection. No new safety signals were identified.

I, the signatory for these applications, concur with the multidisciplinary review team recommendations to approve MAVYRET for the treatment of acute HCV infection.

1.2 Benefit Risk Assessment

The Agency's benefit-risk assessment is summarized below.

Benefit-Risk Assessment Framework

MAVYRET is a fixed-dose combination of glecaprevir (GLE), a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir (PIB), an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 3 years and older with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET (GLE/PIB) is also indicated for the treatment of adult and pediatric patients 3 years and older with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. The original MAVYRET New Drug Application (NDA) was approved on August 3, 2017.

With NDA 209394 S-19 and NDA 215110 S-05, the Applicant seeks to expand the indication to include treatment of acute HCV infection. Chronic HCV infection is a serious and life-threatening medical condition that, if left untreated, can progress over time to severe hepatic and systemic complications, including cirrhosis, liver failure, and hepatocellular carcinoma, potentially resulting in death. While acute HCV infection may resolve spontaneously, the majority of individuals who are diagnosed with acute HCV infection go on to develop chronic HCV infection. According to the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), chronic HCV infection affects approximately 50 million people worldwide, with an estimated one million new infections each year. In the US, an estimated 2.4 million people are chronically infected with HCV, with cases of acute HCV increasing about 2-fold from 2015 through 2022. The increasing incidence reflects new infections associated with rising rates of injection drug use; an estimated 67,400 new HCV infections occurred in 2022. While injection drug use remains the primary risk factor for acute HCV infection in the US, risk of sexual transmission among men who have sex with men (MSM) is also significant, particularly for individuals with human immunodeficiency virus (HIV) co-infection. Globally, unsafe healthcare practices and mother-to-child transmission during pregnancy or childbirth are major contributors to HCV transmission, especially in resource-limited settings and regions with high HCV prevalence.

There is no FDA approved treatment option for acute HCV infection, although treatment for both chronic and acute HCV infection is recommended in US Practice Guidelines (AASLD/IDSA). Prompt initiation of curative antiviral treatment in the setting of acute HCV infection is likely to prevent progression to chronic HCV, reducing the risk of severe liver complications and death for the treated individual. In addition, persons with acute HCV infection often have high HCV viral loads and may continue to participate in activities associated with HCV transmission (e.g., IV drug use, unprotected sex), and therefore could pose a significant risk of viral transmission to unaffected persons. Thus, treatment of individuals diagnosed with acute HCV may reduce the risk of HCV transmission in the broader community, an important public health benefit.

The current standard of care treatments for chronic HCV GT 1-6 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. For chronic HCV infection, GLE/PIB demonstrated SVR12 rates ranging from 91-100% as documented in the original NDA submission review and in subsequent supplement reviews. SVR12 rates varied depending on the regimen, patients' HCV GT, and patients' prior treatment history. The observed efficacy in the original NDA was similar in patients with or without compensated cirrhosis, with or without HIV coinfection, and with chronic kidney disease (CKD), with or without hemodialysis. Efficacy and safety were comparable in people who inject drugs (PWID) and those on medication assisted treatment (MAT) for opioid use disorder.

The current NDA supplements provide safety and efficacy data from the Study M20-350, a Phase 3b multicenter, single-arm, open-label prospective study in which 286 adult participants with acute HCV received MAVYRET for eight weeks. The primary endpoint of the study was the proportion of participants achieving SVR12 compared to an efficacy threshold derived from a weighted average of historical MAVYRET SVR12 rates from participants with chronic HCV infection in Phase 2/3 studies who self-reported injection-drug use status (current/recent PWID or former/non-PWID), subtracting a margin of 6% from the weighted average of the rates. Study participants were predominantly male (90%), white (86%), enrolled in Europe (71%) with a mean age of approximately 44 years. Fifty percent of participants were co-infected with HIV. The risk behavior associated with a majority of acute infections in the study was unprotected sex in men who have sex with men (66%). A low proportion reported injection drug use within 6 months of the study (7%). Most participants were identified with HCV GT1 (58%), GT4 (17%) or GT3 (12%) infection. No participants had GT5 or GT6 infection. The majority of participants were without cirrhosis (97%). At baseline, most participants had elevated alanine transaminase (ALT) and bilirubin levels; thirteen percent had ALT >10 X ULN and four percent had bilirubin levels > 2X ULN.

The efficacy data generated in Study M20-350 showed that the SVR12 rate in the overall ITT population was 96.2% (275/286) with a 95% CI of [93.2%, 97.8%]; the lower bound of the 95% CI was greater than the efficacy threshold of 90.5% for this population. None of the participants who failed to achieve SVR12 had protocol-defined on-treatment virologic failure or post-treatment relapse; two participants had evidence of re-infection in the post-treatment period. The SVR12 rate in this study is comparable to that of MAVYRET and other approved DAAs for the treatment of chronic HCV. The safety profile of acute HCV treatment was comparable to that of chronic HCV treatment and there were no events of liver enzyme or hepatitis flares, liver injury or hepatic decompensation observed on therapy. No new safety or efficacy issues were identified. Efficacy and safety amongst key demographic subgroups were similar to that in the studies of chronic HCV. Of note, based on these favorable efficacy and safety results from Study M20-350 and the lack of FDA-approved treatments for acute HCV infection, MAVYRET for the treatment of acute HCV infection was granted Breakthrough Therapy designation on January 22, 2025.

Although the data reviewed with these supplements were generated in adults, the conclusions are appropriate to extrapolate to pediatric patients ages 3 and older because the course of HCV disease is sufficiently similar between adults and children older than 3 years of age, the response to DAA treatment is similar, and the same dosing regimens were proposed for acute HCV treatment as are already approved for chronic HCV treatment for pediatric patients ages 3 and older. Further, the previously reviewed PK and safety data in adolescents from DORA Part 1 established the exposure and safety of GLE/PIB to be similar between adults and adolescents, and DORA Part 2 established efficacy and safety in participants aged 3 years to less than 12 years in for the MAVYRET oral pellet formulation.

In conclusion, the benefit of MAVYRET for the treatment of acute HCV infection outweighs the risks as demonstrated in Study M20-350. The multidisciplinary review team and CDTL recommend approval of this supplement in adult and pediatric patients 3 years and older based on review of the available evidence of efficacy and safety submitted. Sections 1, 6, 7, 8, 12 and 14 of the USPI were updated to provide data to support the indication of treatment of acute HCV infection.

Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Although acute HCV infection may resolve spontaneously, the majority of individuals diagnosed with acute HCV develop chronic infection. • Chronic HCV infection causes inflammation of the liver that can lead to long-term health problems or death. • Chronic HCV affects 50 million people worldwide, with an estimated one million new infections each year. • In the US, an estimated 2.4 million people are chronically infected with HCV, with cases of acute HCV increasing about 2-fold from 2015 through 2022. • The increasing incidence reflects new infections associated with rising rates of injection drug use; an estimated 67,400 new HCV infections occurred in 2022. • While injection drug use remains the primary risk factor for acute hepatitis C virus (HCV) in the US, risk of sexual transmission among men who have sex with men (MSM) is also significant, particularly for individuals with HIV co-infection. • Globally, unsafe healthcare practices and mother-to-child transmission during pregnancy or childbirth are major contributors to HCV transmission, especially in resource-limited settings and regions with high HCV prevalence.	• If untreated, chronic HCV infection is a serious and life-threatening medical condition. Patients with acute and chronic HCV can experience symptoms that are severe and debilitating and can transmit the infection to others. • Acute HCV infection is a significant public health concern particularly in the context of an ongoing opioid epidemic. • Prompt initiation of curative antiviral treatment in the setting of acute HCV is likely to prevent progression to chronic HCV, reducing the risk of severe liver complications and death for the treated individual. • Treatment of individuals diagnosed with acute HCV may reduce the risk of HCV transmission to others in the broader community, a potentially important public health benefit.
Current Treatment Options	• There is no FDA approved treatment option for acute HCV infection, although treatment for acute HCV infection is recommended in US Practice Guidelines (AASLD/IDSA) using the same regimens recommended for chronic HCV infection (i.e., off-label).	• Labeling the available safety and effectiveness of MAVYRET use in participants with acute HCV infection provides healthcare providers with useful information regarding safety, efficacy, and recommended treatment duration for MAVYRET in acute HCV infection.
Benefit	• The current NDA supplement provided safety data and efficacy data from the Study M20-350, a Phase 3b trial multicenter, single-arm, open-label prospective study in which 286 adult participants with acute HCV received MAVYRET for eight weeks. • The efficacy data generated in Study M20-350 showed that the SVR12 rate in the overall TT population was 96.2% (275/286) with a 95% CI of [93.2%, 97.8%]; the lower confidence bound was greater than the efficacy threshold of 90.5% for this population.	• The data generated in Study M20-350 support the efficacy and safety of MAVYRET for the treatment of acute HCV infection. • The SVR12 rate in this study is similar to that of MAVYRET and other approved DAAs for the treatment of chronic HCV. • The safety profile of acute HCV treatment was similar to that of the treatment of chronic HCV

Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**

	• None of the participants who failed to achieve SVR12 experienced on-treatment virologic failure or relapse.
	• Two participants experienced HCV re-infection in the post-treatment period.
	• No new safety or efficacy issues were identified. There were no liver enzyme or hepatitis flares, liver injury or hepatic decompensation observed on therapy.
	• Efficacy and safety amongst key demographic subgroups were similar to that in the studies of chronic HCV infection.
	  ○ Although the data reviewed with these supplements were in generated adults, the conclusions are appropriate to extrapolate to pediatric patients ages 3 and older for the following reasons:
	  ○ The course of HCV disease is sufficiently similar between adults and children older than 3 years of age.
	  ○ Response to DAA treatment is similar between adults and children older than 3 years of age.
	  ○ The same dosing regimens were proposed for acute HCV treatment as are already approved for chronic HCV treatment for pediatric patients ages 3 and older.
	  ○ Previously reviewed PK and safety data in adolescents from DORA Part 1 established the exposure and safety of GLE/PIB to be similar between adults and adolescents with chronic HCV infection.
	  ○ DORA Part 2 established efficacy and safety in participants aged 3 years to less than 12 years with chronic HCV infection for the MAVYRET oral pellet formulation.
		with MAVYRET.
		• Safety and efficacy conclusions are appropriate to extrapolate to the adolescent and pediatric population.
		• Patients successfully treated for acute HCV infection remain at risk for reinfection.

Risk and Risk Management	• No new safety signals were identified in the review. • Safety and efficacy data for treatment of acute and chronic HCV infection were similar. • Descriptive safety, virology and efficacy data were added to the label to inform providers.	• Safety concerns associated with GLE and PIB use in acute and chronic HCV infection are adequately addressed in product labelling. • The observation of two participants with HCV reinfection in Study M20-350 is described in labeling to alert clinicians of the risk of reinfection.

2. Background

Chronic infection with hepatitis C virus (HCV) is a serious and life-threatening condition. When left untreated, over a period of years to decades, chronic HCV infection can lead to serious liver problems including cirrhosis, hepatic decompensation/failure, hepatocellular carcinoma, and death[1].

Acute HCV infection precedes chronic HCV infection and is generally defined based on HCV serostatus (i.e., typically negative for anti-HCV antibody if not previously infected), positive detection of HCV RNA in blood, fluctuating liver enzyme levels, and timing of known HCV exposure. Although acute HCV infection can be self-limiting and spontaneously cleared within 6 months of initial infection, 60 to 80% of those with acute HCV ultimately develop chronic HCV infection[2]. Men, people of older age, and people with HIV co-infection are more likely to develop chronic HCV infection than women, people of younger age, and people without HIV co-infection[1, 2].

According to the World Health Organization (WHO), chronic HCV infection affects approximately 50 million people worldwide, with about 1 million new infections occurring per year[3]. An estimated 2.4 million people in the United States are chronically infected with HCV[4]. In the US, reported cases of acute HCV infection increased about 2-fold from 2015 through 2022[4, 5]. The increasing incidence reflects new infections associated with rising rates of injection drug use. An estimated 67,400 new HCV infections occurred in 2022; over half of identified cases in 2022 were associated with injection drug use[6]. While injection drug use remains the primary risk factor, other significant risk factors for acute HCV in the US include sexual transmission among men who have sex with men (MSM), particularly those co-infected with HIV[7]. Globally, unsafe healthcare practices, including the reuse of medical equipment and inadequate screening of blood products, continue to be major contributors to HCV transmission in resource-limited settings[8-10]. Additionally, mother-to-child transmission during pregnancy or childbirth is an important route of HCV infection, especially in regions with high HCV prevalence[10, 11].

Prompt initiation of curative antiviral treatment in the setting of acute HCV infection is likely to prevent progression to chronic HCV infection, reducing the risk of severe liver complications and death in treated individuals[12]. In addition, persons with acute HCV infection often have high HCV viral loads and may continue to participate in activities associated with HCV transmission (e.g., IV drug use, unprotected sex), and therefore, pose a significant risk of viral transmission to unaffected persons. Thus, effective treatment of acute HCV infection may reduce the risk of HCV transmission in the community, an important public health benefit[13-16].

The current standard of care treatment for chronic 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.

U.S. treatment guidelines (AASLD/IDSA) currently recommend treating patients with acute HCV infection upon initial diagnosis without awaiting possible spontaneous resolution or progression to chronic HCV infection, essentially using a "test and treat" approach to simplify patient care and minimize loss to follow-up[17]. Multiple published, small-scale studies have reported efficacy (SVR12) of HCV DAA regimens for the treatment of acute or early HCV infection[18-20]. To simplify patient management, treatment guidelines recommend using the same regimens for patients with acute HCV infection that are recommended for patients with chronic HCV infection, as distinguishing between acute versus early chronic HCV infection may be clinically challenging.

Despite being used in the standard-of-care treatment of acute HCV infection, none of the currently approved HCV antiviral treatments are specifically indicated for the treatment of acute HCV infection; the efficacy of all of these regimens was established in the setting of chronic HCV infection. Thus, there is currently an unmet need for FDA-approved therapies to treat acute HCV infection.

MAVYRET is a fixed-dose combination of glecaprevir (GLE), a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir (PIB), an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 3 years and older with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET (GLE/PIB) is also indicated for the treatment of adult and pediatric patients 3 years and older with HCV GT1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. The original MAVYRET New Drug Application (NDA 209394) was approved on August 3, 2017, for the tablet formulation in adults. MAVYRET was subsequently approved for adolescents and children, including a pellet formulation under NDA 215110. See the MAVYRET Prescribing Information for recommended treatment durations for all indicated patient populations.

In patients with chronic HCV infection, MAVYRET (GLE/PIB) demonstrated SVR12 rates ranging from 91-100% for treatment durations recommended by the FDA review team in the original NDA submission and in subsequent supplements. SVR12 rates varied depending on the regimen, patients' HCV GT, and patients' prior treatment history. Efficacy in the original NDA was similar in patients with or without cirrhosis, with or without HIV coinfection, and with chronic kidney disease (CKD), with or without hemodialysis. Efficacy and safety are comparable in children and adolescents, people who inject drugs (PWID) and those on medication assisted treatment (MAT) for opioid use disorder.

The primary purpose of the current sNDAs (NDA 209394 S-19 and NDA 215110 S-05) was to provide available MAVYRET clinical safety and efficacy data from Study M20-350, a Phase 3b, multicenter, single-arm, open-label prospective study in which 286 adult participants with acute HCV infection received MAVYRET for eight weeks, to support the proposed new indication for the treatment of acute HCV infection. The following review provides a comprehensive assessment of these data supporting the new indication of treatment of acute HCV infection for MAVYRET.

3. Product Quality

No new biopharmaceutics information (e.g., formulation or dissolution data) is included with NDA 208394 S-19 or NDA 215110 S-5. No quality inspections of manufacturing and testing sites were required as these sites were inspected during review of the original NDAs.

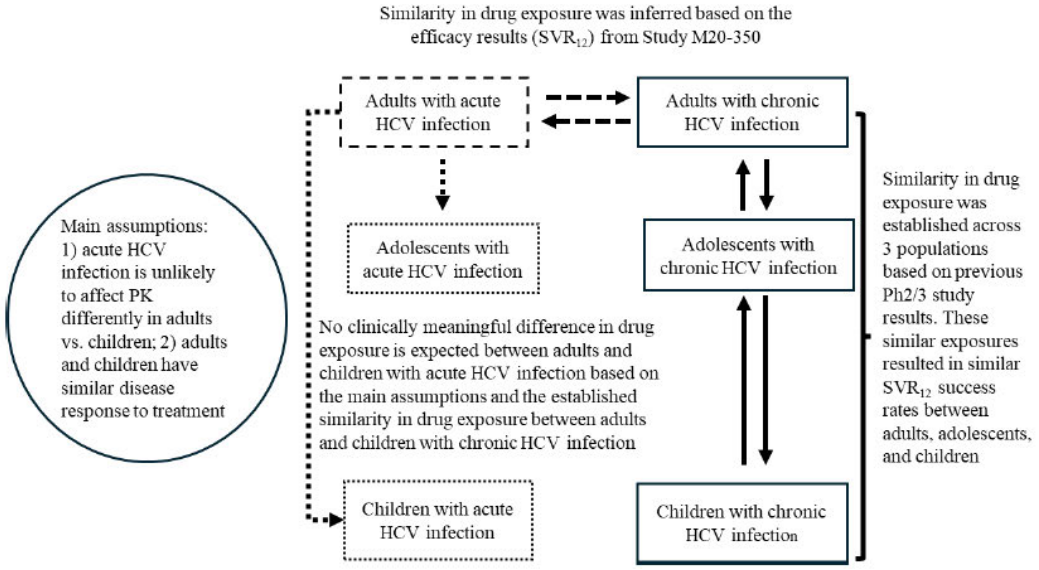
4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information is included with NDA 208394 S-19 or NDA 215110 S-5.

5. Clinical Pharmacology

No new pharmacokinetic data in either adults or pediatric patients with acute HCV infection were included in NDA 208394 S-19 or NDA 215110 S-5. While the efficacy and safety of MAVYRET for acute HCV infection has been demonstrated in the Phase 3 Study M20-350 in adults, the efficacy and safety in pediatric patients age from 3 years to < 18 years with acute HCV infection were proposed to be extrapolated from adults. **Figure 1** below summarizes the rationale from the applicant regarding extrapolating efficacy and safety from adults with acute HCV infection to pediatric patients.

Figure 1. Extrapolation Approach



Note: Solid line rectangles indicate populations where both efficacy and exposure data are available; dashed line rectangle indicates a population where efficacy data are available but without exposure data; dotted line rectangles indicate populations where no data are available. Solid arrows show that similarity of exposures has been established; dashed arrows show that similarity of exposures has been inferred based on similar efficacy; dotted arrows show extrapolation of exposure and efficacy.

Source: Applicant. Module 2, Summary of Clinical Pharmacology Studies, Figure 2

The Clinical Pharmacology team agree with the applicant's extrapolation proposal based on the evidence shown below.

- Assumed similar disease progression and response to the MAVYRET treatment in adults and pediatric patients with acute HCV infection.
- The same dosing regimen was proposed for adult and pediatric patients with acute or chronic HCV infection.
- Similar plasma exposure of glecaprevir and pibrentasvir were observed in adult and pediatric patients with chronic HCV infection following labeling recommended doses. Please refer to Table 9 in the current MAVYRET label[1] for detail.

See **Pediatrics (Section 8)** for a summary of the data submitted to support extrapolation of study data to pediatric populations for the proposed indication for the treatment of acute HCV infection.

6. Clinical/Statistical- Efficacy

6.1 Study Design

Summary of Trial Design and Participant Population
Study M20-350 was a Phase 3b, multicenter, single-arm, prospective study designed to evaluate the safety and efficacy of 8 weeks of GLE/PIB treatment in adult and adolescent participants ≥ 12 years of age with physician-diagnosed acute HCV infection, with no prior treatment for the current infection, and with no cirrhosis or with compensated cirrhosis. Participants were further required to have no evidence of chronic HCV infection or hepatitis B virus infection. Participants with HIV-1 co-infection and people who inject drugs (PWID) currently were permitted to participate. Approximately 283 participants were planned for enrollment. Although the study design included adolescents, no adolescents were enrolled.

The study consisted of an 8-week open-label treatment period followed by a 12-week post-treatment period, as shown in the below study schematic (**Figure 2**).

Figure 2. Schematic for Study M20-350

[1] www.accessdata.fda.gov/drugsatfda_docs/label/2023/209394s016,215110s003lbl.pdf assessed on 5/5/2025

Source: Applicant. Statistical analysis plan, Figure 1.

The doses of GLE (300 mg) and PIB (120 mg) used in this study are the approved doses for treatment of chronic HCV infection, which were predicted to be similarly effective in treating acute HCV infection.

Summary Diagnostic Entry Criteria (Acute HCV infection)
Diagnostic criteria included physician-diagnosed acute HCV infection, quantifiable HCV RNA at Screening, and at least 1 of the following:

- Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; OR
- Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen; OR
- Clinical signs and symptoms compatible with acute hepatitis (ALT >5× upper limit of normal [ULN] and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen; OR
- Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening.

Efficacy Endpoints
The primary efficacy endpoint and the key secondary efficacy endpoint were achievement of SVR12 in the intent-to-treat (ITT) and modified intent-to-treat with virologic failure (mITT-VF) populations, respectively (see Analysis Set definitions below). Achievement of SVR12 was defined as HCV RNA < LLOQ 12 weeks after last actual dose of study treatment.

- Supportive secondary endpoints were on-treatment virologic failure (OTVF), post-treatment relapse as of post-treatment Week 12 (relapse12), and post-treatment reinfection with HCV in the ITT population.
- Additional efficacy endpoints were achievement of HCV RNA < LLOQ at each post-baseline visit in the Treatment Period, achievement of SVR4 (i.e., SVR at 4 weeks post-treatment), virologic failure through post-treatment Week 12, and Relapse overall in the ITT population.

Safety Endpoints
Safety objective endpoints were as follows for each participant in the safety analysis set:

- ALT elevations of NCI CTCAE Version 4.03 Grade 1, 2, 3, or 4 during the Treatment Period with ALT grade increased from Baseline.
- Post-nadir ALT elevation > 3 × ULN with total bilirubin > 2 × ULN during the Treatment Period.
- Treatment-emergent hepatic decompensation/hepatic failure events.
- Treatment-emergent Adverse Events (AEs) leading to discontinuation of study treatment.

- Treatment-emergent Severe Adverse Events (SAEs).

Analysis Sets:

- The ITT analysis set was defined as all enrolled participants who received at least 1 dose of study treatment.
- The mITT-VF analysis set was defined as all enrolled participants who received at least 1 dose of study treatment, excluding those who did not achieve SVR12 for reasons other than virologic failure (i.e., those with HCV reinfection, those who did not achieve SVR12 due to early premature discontinuation of study treatment, and those who were missing HCV RNA data in the SVR12 window after backward imputation).
- The safety analysis set was defined as all participants who received at least 1 dose of study treatment.

Statistical Methods
Primary endpoint: The number and percentage of participants who achieved SVR12 were calculated along with a 2-sided 95% confidence interval (CI) using Wilson's score method. The threshold for comparison for the primary efficacy endpoint was calculated as a weighted average of historical GLE/PIB ITT SVR12 rates from participants with chronic HCV infection in Phase 2/3 studies who self-reported as PWID currently or recently (current/recent PWID) with SVR12 rate 88.7% (55/62), and those who self-reported as formerly or never injecting drugs (former/non-PWID) with SVR12 rate 97.8% (4147/4241), subtracting a margin of 6%. Here the weights were the proportion of current/recent PWID participants and the proportion of former/non-PWID participants in the ITT population of study M20-350.

The margin of 6% was selected to ensure a minimal loss of efficacy of the 8-week GLE/PIB regimen in acute HCV infection relative to the historical SVR12 rate in participants with chronic HCV infection. This was agreed between the Agency and the Applicant during the study design, and the 6% is not a non-inferiority (NI) margin. The primary analysis should be interpreted as a superiority comparison to a chosen SVR12 threshold using the lower bound of the 95% CI for the SVR12 for GLE/PIB.

The weights were based on the proportions of current/recent PWID participants and former/non-PWID participants in Study M20-350, which leads to the following formula:

Efficacy threshold = (Proportion of current/recent PWID × 88.7%) + (Proportion of former/non PWID× 97.8%) - 6%.

The classification of current/recent PWID and former/non-PWID was conducted using a PWID classification criteria (denoted by PWID status classification 1), which was defined with respect to study treatment start (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID). The details of this PWID status classification 1 and the PWID status classifications 2 and 3 discussed later can be found in the Appendix. Here PWID status classification 1 was used to derive the efficacy threshold for primary analysis, which leads to an efficacy threshold of 90.5%= (0.143×88.7%) + (0.857×97.8%) - 6%.

Superiority to the efficacy threshold would be demonstrated if the lower bound of the 2-sided 95% CI derived by Wilson's score method for the percentage of subjects who achieved SVR12 was greater than the threshold (90.5%). The attributes of the primary endpoint estimand were listed in the **Table 1** below.

Table 1. Attributes of the primary endpoint estimand

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary	GLE/PIB 8 Weeks	SVR_{12}	ITT	Subjects who discontinue the study with an unknown SVR_{12} status (after applying backward imputation) will be counted as a failure for SVR_{12}	Number and percentage of subjects who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method[2]

Source: Applicant. Statistical Analysis Plan, Table 2.

Sensitivity analysis of primary endpoint: As Wilson's score method was an approximation-based method, the statistical reviewer also used the Clopper-Pearson's method to derive the exact 2-sided 95% CI and examined the robustness of the results via Wilson's score method.

Supplementary analyses of the primary endpoint: Besides using the PWID classification defined with respect to study treatment start (PWID status classification 1), the Applicant also used different PWID classification criteria, including PWID classification 2 defined with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID), and PWID Status Classification 3 defined with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID), to derive the efficacy thresholds for supplementary analyses of the primary endpoint of participants in the ITT population.

Additionally, the Applicant also conducted supplementary analyses to compare the number and percentage of participants in the ITT population with baseline HCV RNA ≥ LLOQ who achieve SVR12 along with a two-sided 95% CI derived by Wilson's score method. The lower bound of the 95% CI was compared to the efficacy threshold as calculated using the proportions of PWID and non-PWID participants in the ITT population with baseline HCV RNA ≥LLOQ derived through the PWID status classifications 1, 2, and 3, respectively. Note there were two participants who had missing baseline HCV RNA values, and the Applicant used their HCV RNA value at screening visit to impute the missing values at baseline visit. The review team hence conducted sensitivity analyses in a similar way but restricted the

mITT-VF population with HCV RNA ≥ LLOQ to those who without missingness at the baseline.

Key secondary endpoint: The threshold for comparison for the key secondary efficacy endpoint was calculated in the same manner as the calculation for the primary efficacy endpoint except that it was based on historical GLE/PIB mITT-VF (rather than ITT) SVR12 rates, and the 2-sided 95% CI was derived using Wilson's score method. Specifically, the SVR12 rate of current/recent PWID participants in the mITT-VF populations of the historical studies was 98.2% (55/56), and for former/non-PWID participants the SVR12 rate was 98.8% (4147/4197). Here the weights were the proportion of current/recent PWID participants and the proportion of former/non-PWID participants in the mITT-VF population of study M20-350, which ultimately led to the efficacy threshold of 92.7% = (0.131× 98.2%) + (0.869× 98.8%) − 6%.

A fixed-sequence testing procedure was used for the primary and key secondary efficacy endpoints; the key secondary endpoint was to be assessed for superiority to the threshold only if the primary efficacy endpoint was achieved. The attributes of the key secondary endpoint estimand were listed in the **Table 2** below. Subgroup analyses were performed for subgroup variables such as baseline HCV/HIV-1 co-infection status.

Table 2. Attributes of the key secondary endpoint estimand

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Key Secondary	GLE/PIB 8 Weeks	SVR_{12}	mITT-VF	Not applicable	Number and percentage of subjects who achieve SVR_{12} along with a two-sided 95% CI calculated using Wilson's score method[2]

Source: Applicant. Statistical Analysis Plan, Table 3.

Sensitivity analysis of key secondary endpoint: As Wilson's score method was an approximation-based method, the statistical reviewer also used the Clopper-Pearson's method to derive the exact 2-sided 95% CI and examine the robustness of the results via Wilson' score method.

Supplementary analyses of key secondary endpoint: Besides using the PWID classification defined with respect to study treatment start (PWID Status Classification 1), the Applicant also used different PWID classification criteria, including PWID classification 2 defined with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID,

recent PWID, former PWID, or non-PWID), and PWID Status Classification 3 defined with respect to study treatment period (current/recent PWID or former/non-PWID; current PWID, recent PWID, former PWID, or non-PWID), to derive the efficacy threshold for supplementary analyses of the key secondary endpoint of participants in the mITT-VF population.

Additionally, the Applicant conducted supplementary analyses to compare the number and percentage of subjects in the mITT-VF population with baseline HCV RNA ≥ LLOQ who achieve SVR12 along with a two-sided 95% CI derived by Wilson's score method. The lower bound of the 95% CI was compared to the efficacy threshold as calculated using the proportions of PWID and non-PWID participants in the mITT-VF population with baseline HCV RNA ≥ LLOQ derived through the PWID status classifications 1, 2, and 3, respectively. Note here there were two participants with missing baseline HCV RNA values, and the Applicant used their HCV RNA value at screening visit to impute the missing values at baseline visit. The review team hence conducted sensitivity analyses in a similar way but restricted the mITT-VF population with HCV RNA ≥ LLOQ to those who without missingness at the baseline.

Missing data handling: For analyses of SVR results (e.g., SVR4, SVR12), backward imputation applied to participants' missing visit values. Specifically, if the nearest HCV RNA value after the SVR window was <LLOQ (unquantifiable or not detected), then it was used to impute the HCV RNA value in the SVR window. If a participant was missing an HCV RNA value within the appropriate SVR window after performing backward imputation, then this value was imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value was assigned as missing. A participant with missing HCV RNA data in the analysis window, after backward imputations, was imputed as a failure.

Supportive secondary endpoints: OTVF, Relapse12, and post-treatment reinfection with HCV were summarized by number and percentage of participants in the ITT population along with a two-sided 95% CI calculated using Wilson's score method.

Subgroups analyses: Subgroup analyses were conducted on both the ITT population and mITT-VF population for SVR12 and other supportive endpoints mentioned above. Note here for deriving the efficacy threshold of a given subgroup, the weights were the proportions of current/recent PWID participants and former/non PWID in this subgroup.

Safety: The safety analysis set was used for all safety analyses and consisted of all participants who received at least 1 dose of study treatment. Treatment-emergent AEs, defined as those with onset during GLE/PIB treatment through 30 days post-dosing, were summarized with number and percentage of participants. The number and percentage of participants with laboratory values during treatment meeting toxicity grade and potential hepatotoxicity criteria were summarized. Hepatic decompensation/hepatic failure events were identified using the AbbVie Product Medical Dictionary for Regulatory Activities (MedDRA) query, including events such as ascites, hepatic encephalopathy, esophageal variceal bleeding, and spontaneous bacterial peritonitis. For each safety objective endpoint, the number and percentage of participants who met the criteria were calculated. MedDRA version 27.0 was used.

Clinical Virology Laboratory Procedures
Plasma samples for analyses of HCV RNA levels were obtained at Screening, Baseline, Weeks 2, 4 and 8 (end-of-treatment), and Post-Treatment Weeks (PTWs) 4 and 12. Samples were also collected at these visits, except Screening, for possible HCV drug resistance analyses.

Plasma HCV RNA levels were measured in a central laboratory (b) (4) using the Roche COBAS® AmpliPrep/COBAS® TaqMan® Quantitative HCV Test, v2.0. The LLOQ and limit of detection for the assay were both 15 IU/mL.

HCV genotypes and subtypes were assessed at Screening in the central laboratory using the Versant HCV Genotype Inno-LiPA Assay v2.0 (Line Probe Assay [LiPA]) or based on a Sanger population nucleotide sequencing assay targeting the viral NS5B gene. In addition, HCV genotypes and subtypes in baseline samples were confirmed or further refined retrospectively by the sponsor based on phylogenetic analysis of the NS3 and/or NS5A genes. Additional selected samples were analyzed for HCV genotype/subtype determination to determine if SVR12 failure might be explained by reinfection with another HCV genotype, subtype or clade.

Other Clinical Virology-related assessments at Screening included qualitative assessment of anti-HCV antibody, anti-HIV antibody and hepatitis B virus surface antigen (HBsAg).

For resistance analyses, next generation sequencing (NGS) was conducted on plasma samples targeting the HCV NS3/4A and NS5A genes for all baseline samples and for selected post-baseline samples for participants who experienced virologic failure or possible HCV reinfection. Only samples with HCV RNA levels ≥1,000 IU/mL were sequenced. According to the resistance dataset, NGS was based on the Illumina Miseq platform, and amino acid sequences were reported relative to subtype-specific reference strains. A ≥2% sensitivity cutoff was used for reporting amino acid differences from reference in the dataset; however, a 15% sensitivity cutoff was used for analysis of baseline HCV polymorphisms and their impact on treatment outcomes, which is consistent with prior analyses of GLE/PIB and other HCV DAA-based regimens. Independent FDA analyses of resistance data were conducted on the sponsor's analysis-ready dataset but did not include analysis of raw NGS fastq data.

6.2 Participant Disposition

The statistical review team was able to confirm the Applicant's participant disposition results.

A total of 286 participants were enrolled/treated at 70 sites in 8 countries. All 286 participants were included in the ITT analysis set. The disposition of ITT participants, listed in the following **Table 3**, indicated that eight participants discontinued from the study treatment. The reasons for the eight participants who discontinued study treatment are listed in **Table 3**; no participant discontinued due to efficacy-related reasons.

Table 3. Disposition of participants and reasons for discontinuation for ITT

Disposition of participants		
	Number of participants (ITT)	Number of participants (mITT-VF)
Enrolled/Treated	286	275
Study treatment disposition		
Completed study treatment	278	272
Discontinued study treatment	8	3
Study disposition		
Complete study	278	272
Discontinued study	8	3
Reasons for discontinuation from study treatment		
	Number (%) of participants (ITT, N=286)	Number (%) of participants (mITT-VF, N=286)
Discontinuation for any reason	8 (2.8)	3 (1.1)
Primary reason for discontinuation		
Adverse event	1 (0.3)[a]	1 (0.4)[a]
Lost to follow-up	3 (1.0)	0
Lack of efficacy	0	0
Withdrawal from treatment by participant	1 (0.3)	0
Non-compliance with study treatment	3 (1.0)	2 (0.7)
Other	0	0

[a] Event was considered to have no reasonable possibility of relationship to study treatment per the investigator.
Source: FDA Reviewer. Applicant table reproduced by review team using ADSL.xpt.

6.3 Enrollment Failures and Protocol Deviations

The clinical reviewer performed an analysis of enrollment failures and protocol deviations.

Seventy-three individuals were screened but excluded and considered enrollment failures. Sixty-seven enrollment failures were determined to not meet eligibility criteria (i.e., were screen failures). Among the 6 enrollment failures who met eligibility criteria at screening, 3 were determined later by the site to no longer have acute HCV, 1 was lost to follow-up, 1 withdrew consent, and 1 did not return to the site to receive study treatment after a delay in delivery of the study drug.

Significant protocol violations were reported in relation to 28 (9.8%) participants. As shown in in **Table 4** below, most protocol deviations were in the category of eligibility criteria, including missed screening laboratories, misclassification of at least one entry criteria, required SARS Cov-2 testing not being completed, and a delayed classification of liver decompensation status.

Table 4. Significant Protocol Deviations: Safety Analysis Set

Deviation	Number (%) of Subjects (N = 286)
Any significant deviation	28 (9.8)
Type of deviation[a]	
Eligibility criteria not met	22 (7.7)
Required screening laboratory tests not performed	6 (2.1)
Lack of evidence of acute HCV infection	7 (2.4)[b]
SARs-CoV-2 test not done	9 (3.1)
History of liver decompensation	1 (0.3)[c]
Withdrawal criteria developed but subject not withdrawn	0
Wrong treatment or incorrect dose of study treatment received	0
Prohibited concomitant medication used	6 (2.1)

a. Subjects may have had more than 1 deviation or failed to meet more than 1 eligibility criterion; therefore, the sum of the counts given for the type of deviation or the eligibility criteria not met may be greater than the overall number of subjects with any deviation or with eligibility criteria not met, respectively.

b. Six subjects failed to satisfy at least 1 of criteria a – d (Table 7); 1 additional subject did not have quantifiable HCV RNA at Screening.

c. Subject had no history of liver decompensation, but at the time of screening, laboratory results were unable to confirm compensated cirrhosis. At Baseline, it was confirmed that the subject had compensated cirrhosis.

Cross reference: Table 14.1__1.6

Source: Applicant, CSR Table 5.

The clinical reviewer determined that neither the enrollment failures nor protocol violations significantly influenced the study's safety, outcome, interpretation of results, or final conclusions.

6.4 Baseline Demographics

The Applicant's demographics were confirmed by the statistical review team.

The selected demographic and baseline characteristics of the ITT population were presented in the following **Table 5** and **Table 6**, respectively.

As shown in **Table 5**, the majority of ITT participants were male (89.2%) and white (86%). The median age of participants was 43 years (range: 20 to 78). 9.4% of the participants had a BMI of at least 30 kg per m^2, 71% of the participants were from Europe, 28.3% were from North America, and 0.7% were from the rest of the world.

As shown in **Table 6**, 57.7% of the participants had HCV genotype 1, 4% had HCV genotype 2, 11.5% had HCV genotype 3, and 16.8% had HCV genotype 4. The median HCV RNA (log_{10} IU/mL) level at baseline is 5.37 (range: 1.17 to 7.57), and 95.8% (274/286) of the participants had HCV RNA at baseline ≥LLOQ, of whom 39% (108/274) had a documented result of negative HCV antibody or unquantifiable HCV RNA within the previous year (subjects classified as "likely acute HCV" (N=62) or "likely acute or early chronic HCV"

(N=46) for the infection stage at baseline). Additionally, two percent of the participants had cirrhosis, 82% of the participants had no history of prior HCV infection, and 49.7% had HCV/HIV-1 coinfection. For PWID status classifications 1, 2, and 3, the differences were minor in terms of proportions.

In a post-hoc exploratory analysis per Agency's request, the Applicant reclassified M20-350 study participants' HCV infection status at baseline based on HCV-specific virology and serology laboratory results alone, as a supplement to current criteria for identifying the acute HCV infection. The percentages of reclassified HCV infection status at baseline are shown in **Table 6.** Details of these reclassification criteria, their rationale, and additional related analyses can be found in **Table 9** in **Section 6.3.3** and **Clinical Virology Section 7.1**.

Table 5. Selected demographic characteristics of ITT population

	Current/recent PWID[a] (N=41)	Former/non-PWID[a] (N=245)	Overall (N=286)
Sex, n (%)			
Female	7 (17.1%)	24 (9.8%)	31 (10.8%)
Male	34 (82.9%)	221 (90.2%)	255 (89.2%)
Race, n (%)			
Asian	2 (4.9%)	5 (2.0%)	7 (2.4%)
Black Or African American	2 (4.9%)	28 (11.4%)	30 (10.5%)
Multiple	2 (4.9%)	1 (0.4%)	3 (1.0%)
White	35 (85.4%)	211 (86.1%)	246 (86.0%)
Ethnicity, n (%)			
Hispanic or Latino	7 (17.1%)	69 (28.2%)	76 (26.6%)
Not Hispanic or Latino	34 (82.9%)	176 (71.8%)	210 (73.4%)
Age (years), n (%)			
Mean (SD)	39.6 (9.81)	44.3 (11.9)	43.7 (11.7)
Median [Min, Max]	38.0 [24.0, 60.0]	44.0 [20.0, 78.0]	43.0 [20.0, 78.0]
Age (years), n(%)			
18 to < 40	23 (56.1%)	86 (35.1%)	109 (38.1%)
40 to < 65	18 (43.9%)	143 (58.4%)	161 (56.3%)
65 to < 75	0 (0%)	15 (6.1%)	15 (5.2%)

	Current/recent PWID[a] (N=41)	Former/non-PWID[a] (N=245)	Overall (N=286)
>= 75	0 (0%)	1 (0.4%)	1 (0.3%)
Age (years), n (%)			
< 65	41 (100%)	229 (93.5%)	270 (94.4%)
>= 65	0 (0%)	16 (6.5%)	16 (5.6%)
Body mass index (kg/m^2), n (%)			
< 30	40 (97.6%)	219 (89.4%)	259 (90.6%)
>= 30	1 (2.4%)	26 (10.6%)	27 (9.4%)
Country, n (%)			
Austria	3 (7.3%)	4 (1.6%)	7 (2.4%)
Canada	2 (4.9%)	11 (4.5%)	13 (4.5%)
France	1 (2.4%)	17 (6.9%)	18 (6.3%)
Germany	13 (31.7%)	59 (24.1%)	72 (25.2%)
Italy	5 (12.2%)	12 (4.9%)	17 (5.9%)
Spain	8 (19.5%)	81 (33.1%)	89 (31.1%)
United States	9 (22.0%)	59 (24.1%)	68 (23.8%)
Australia	0 (0%)	2 (0.8%)	2 (0.7%)
Geographic region, n (%)			
Europe	30 (73.2%)	173 (70.6%)	203 (71.0%)
North America	11 (26.8%)	70 (28.6%)	81 (28.3%)
Rest of World	0 (0%)	2 (0.8%)	2 (0.7%)
Alcohol use, n (%)			
Current	21 (51.2%)	143 (58.4%)	164 (57.3%)
Former	10 (24.4%)	30 (12.2%)	40 (14.0%)
Never	10 (24.4%)	67 (27.3%)	77 (26.9%)
Missing/unknown	0 (0%)	5 (2.0%)	5 (1.7%)

[a] based on PWID status classification 1.
Source: FDA Reviewer. Table produced using ADSL.xpt, ADEFFOUT.xpt.

Table 6: Selected baseline characteristics of ITT populations

	Current/recent PWID[a] (N=41)	Former/non-PWID[a] (N=245)	Overall (N=286)
HCV genotype[b], n (%)			
1	20 (48.8%)	145 (59.2%)	165 (57.7%)
2	1 (2.4%)	10 (4.1%)	11 (3.8%)
3	10 (24.4%)	23 (9.4%)	33 (11.5%)
4	5 (12.2%)	43 (17.6%)	48 (16.8%)
Missing	5 (12.2%)	24 (9.8%)	29 (10.1%)
HCV RNA (log_{10} IU/mL)			
Mean (SD)	4.98 (1.65)	5.01 (1.64)	5.00 (1.64)
Median [Min, Max]	5.33 [1.36, 7.39]	5.37 [1.17, 7.57]	5.37 [1.17, 7.57]
HCV RNA (IU/mL)[c], n (%)			
>= LLOQ	41 (100%)	233 (95.1%)	274 (95.8%)
< LLOQ	0 (0%)	12 (4.9%)	12 (4.2%)
HCV RNA (IU/mL)[d], n (%)			
>= LLOQ	40 (97.6%)	232 (94.7%)	272 (95.1%)
Missing	1 (2.4%)	1 (0.4%)	2 (0.7%)
< LLOQ	0 (0%)	12 (4.9%)	12 (4.2%)
ALT (U/L)			
Mean (SD)	227 (256)	228 (293)	228 (288)
Median [Min, Max]	121 [17.0, 951]	138 [9.00, 2000]	137 [9.00, 2000]
Cirrhosis status, n (%)			
Cirrhotic	1 (2.4%)	4 (1.6%)	5 (1.7%)

	Current/recent PWID[a] (N=41)	Former/non-PWID[a] (N=245)	Overall (N=286)
Non-cirrhotic	40 (97.6%)	238 (97.1%)	278 (97.2%)
Unknown-test results indeterminate	0 (0%)	3 (1.2%)	3 (1.0%)
History of a prior HCV infection			
No	29 (70.7%)	205 (83.7%)	234 (81.8%)
Yes	12 (29.3%)	40 (16.3%)	52 (18.2%)
HCV/HIV-1 co-infection, n (%)			
HCV mono-infected	19 (46.3%)	125 (51.0%)	144 (50.3%)
HCV/HIV-1 co infected	22 (53.7%)	120 (49.0%)	142 (49.7%)
PWID status classification 1[e], n (%)			
Current/recent PWID	41 (100%)	0 (0%)	41 (14.3%)
Former/non-PWID	0 (0%)	245 (100%)	245 (85.7%)
PWID status classification 2[f], n (%)			
Current/recent PWID	41 (100%)	2 (0.8%)	43 (15.0%)
Former/non-PWID	0 (0%)	243 (99.2%)	243 (85.0%)
PWID status classification 3[g], n (%)			
Current/recent PWID	41 (100%)	4 (1.6%)	45 (15.7%)
Former/non-PWID	0 (0%)	241 (98.4%)	241 (84.3%)
Use of MAT for opioid use disorder, n (%)			
No	30 (73.2%)	222 (90.6%)	252 (88.1%)
Yes, 6 to 12 months prior to start of study drug	1 (2.4%)	0 (0%)	1 (0.3%)
Yes, less than 6 months prior to start of study drug	2 (4.9%)	1 (0.4%)	3 (1.0%)
Yes, ongoing at start of study drug	8 (19.5%)	13 (5.3%)	21 (7.3%)
Unknown	0 (0%)	6 (2.4%)	6 (2.1%)
Yes, more than 12 months prior to start of study drug	0 (0%)	3 (1.2%)	3 (1.0%)

	Current/recent PWID[a] (N=41)	Former/non-PWID[a] (N=245)	Overall (N=286)
Infection status at baseline[h], n (%)			
Likely Acute HCV	13 (31.7%)	49 (20.0%)	62 (21.7%)
Likely Acute or Early Chronic HCV	9 (22.0%)	37 (15.1%)	46 (16.1%)
Likely Chronic HCV	2 (4.9%)	4 (1.6%)	6 (2.1%)
Unclear Based on Virology/Serology Alone	17 (41.5%)	143 (58.4%)	160 (55.9%)
Spontaneous HCV Clearance	0 (0%)	12 (4.9%)	12 (4.2%)

[a] based on PWID status classification 1.
[b] Final available GT from phylogenetic analysis or central laboratory if phylogenetic result was not available, per the Applicant.
[c] Two participants' missing values at baseline were imputed using available values collected at screening.
[d] Two participants' missing values at baseline were not imputed and classified as missing.
[e] PWID status classification 1 defined with respect to study treatment start.
[f] PWID status classification 2 defined with respect to study treatment period.
[g] PWID status classification 3 defined with respect to study treatment participation.
[h] Classification of M20-350 study participants' HCV infection status at Baseline based on HCV-specific virology and serology laboratory results alone.
Source: FDA reviewer. Produced using ADSL.xpt, ADEFFOUT.xpt, and LB.xpt.

6.5 Efficacy Results

The statistical review team was able to confirm the Applicant's primary and key secondary efficacy results.

6.5.1 Analysis of Primary Endpoint

The primary analysis was conducted on the ITT population (N=286). The primary analysis results are shown in **Table 7** below. The 95% CIs of SVR12 rate in ITT derived by Wilson's score method (primary analysis) and Clopper Pearson method (sensitivity analysis for primary endpoint) were very similar, resulting in the same lower bound of the 95% CI that was greater than the efficacy threshold of 90.5%, derived by PWID status classification 1, as discussed in Section 6.1. The trial demonstrated a superiority of 8-week GLE/PIB treatment regimen in acute HCV infection over a chosen SVR12 threshold.

Besides using the PWID status classification 1 in ITT to derive the efficacy threshold for primary analysis, the Applicant also used PWID status classifications 2 and 3 in ITT to derive the efficacy thresholds as supplementary analyses of primary endpoint. The recalculated

efficacy thresholds for PWID classifications 2 and 3 were the same (90.4%), similar to the efficacy threshold used for primary analysis (90.5%), and below the lower bounds derived by Wilson's Score method and Clopper Pearson method.

The Applicant also conducted additional supplementary analyses on the ITT population with baseline HCV RNA ≥ LLOQ, resulting in 274 participants. Note that there were two participants with missing HCV RNA values at baseline, and their values at screening were used to impute the missing values at baseline. Using Wilson's score method, the analysis results for SVR12 rate were 96.0% (263/274, 95% CI: 93.0%, 97.7%), where the 95% CI was quite similar to the 95% CI derived by the Clopper Pearson method (95% CI: 92.9%, 97.8%). The lower bounds of 95% CIs derived by both methods were greater than the efficacy thresholds derived by PWID status classifications 1, 2, and 3 in ITT population with baseline HCV RNA > LLOQ, which were 90.4%, 90.4%, and 90.3%, respectively. Specifically, the efficacy thresholds are derived by the following formula:

Efficacy threshold= (Proportion of current/recent PWID in the ITT population with baseline HCV RNA ≥LLOQ x 88.7%) + (Proportion of former/non PWID in the ITT population with baseline HCV RNA ≥ LLOQ x 97.8%) - 6%.

The review team also conducted sensitivity analyses by only including subjects in the ITT population who did not have missing HCV RNA values at baseline and HCV RNA ≥ LLOQ. Those participants who had missing baseline HCV RNA values were excluded from these analyses. The SVR12 rate was 96% (261/272), with Wilson's score 95% CI of (92.9%, 97.7%), and Clopper Pearson 95% CI of (92.9%, 98.0%). Both lower bounds of 95% CI were higher than the efficacy thresholds 90.5%, 90.4%, and 90.4%, derived by PWID status classifications 1, 2, and 3 on the restricted population, respectively, which were consistent with the primary efficacy results.

Table 7: Results of primary and key secondary analyses

Analyses	Analysis sets	Efficacy thresholds (derived using PWID status classification 1)	SVR12 rate (n/N, Wilson Score 95% CI)	Clopper Pearson 95% CI
Primary	ITT	90.5%	96.2% (275/286, 95% CI: 93.2%, 97.8%)	95% CI: 93.2%, 98.1%
Key Secondary	mITT-VF	92.7%	100% (275/275, 95% CI: 98.6%, 100.0%)	95% CI: 98.7%, 100%

Source: FDA Reviewer. Produced using ADSL.xpt, ADEFFOUT.xpt

6.5.2 Analysis of Secondary Endpoints(s)

Results of Analyses of Key Secondary Endpoint

The key secondary analysis was conducted on the mITT-VF population (N=275). The key secondary analysis results are also shown in **Table 7**. The 95% CIs of SVR12 rate in the

mITT-VF population derived by Wilson's score method (key secondary analysis) and Clopper Pearson method (sensitivity analysis for key secondary endpoint) were very similar, resulting in similar lower bounds of the 95% CI, 98.6% and 98.7%, respectively. Both lower bounds were greater than the efficacy threshold of 92.7%, derived by PWID status classification 1, as discussed in Section 6.1. This result demonstrated superiority of an 8-week GLE/PIB treatment regimen in acute HCV infection over a chosen SVR12 threshold for this key secondary endpoint.

Besides using the PWID status classification 1 in the mITT-VF population to derive the efficacy threshold for the key secondary endpoint, the Applicant also used PWID status classifications 2 and 3 in the mITT-VF population to derive the efficacy thresholds as supplementary analyses of the key secondary endpoint. The resulting efficacy thresholds for classifications 2 and 3 were the same (92.7%) and are less than the lower bounds derived by Wilson's Score method and Clopper Pearson method.

Additional supplementary analyses also conducted by the Applicant on mITT-VF participants with baseline HCV RNA > LLOQ, resulting in 263 participants. Note that there were two participants with missing HCV RNA values at baseline, and their values at screening were used to impute the missing values at baseline. Using Wilson's score method, the analysis results for SVR12 rate were 100% (263/263, 95% CI: 98.6%, 100.0%), where the 95% CI was the same as the 95% CI derived by Clopper Pearson method (95% CI: 98.6%, 100%). The lower bounds of 95% CIs derived by both methods were greater than the efficacy thresholds derived by PWID status classifications 1, 2, and 3 in the mITT-VF population with baseline HCV RNA > LLOQ, which all were 92.7%, respectively.

The review team also conducted sensitivity analyses by restricting the analysis population to those subjects in the mITT-VF population who did not have missing HCV RNA values at baseline and HCV RNA ≥ LLOQ. The SVR12 rate was 100% (261/261), with Wilson's score 95% CI of (98.5%, 100%), and Clopper Pearson 95% CI of (98.6%, 100%). Both lower bounds of 95% CIs were higher than the efficacy threshold of 92.7%, derived either by PWID status classifications 1, 2, or 3 on the restricted population, respectively.

Results of Analyses of Supportive Secondary Endpoints

Supportive secondary endpoints include OTVF, Relapse12, and post-treatment reinfection with HCV in the ITT population. No participant experienced OTVF or Relapse12, and only two participants experienced post-treatment reinfection (0.7%, Wilson's score 95% CI: 0.2%, 2.5%).

6.5.3 Subgroup analyses for the primary efficacy endpoint

The SVR12 rates were generally high and consistent across subgroups by demographic, baseline clinical, or virologic characteristics. Selected subgroup analyses are presented in **Tables 8 and 9** below, using both Wilson's score method and Clopper Pearson method to

construct two-sided 95% CI. Subgroup analyses of infection stage at baseline determined by HCV-specific virology and serology laboratory results alone are presented in **Table 9**.

Of note, the sample sizes for many subgroups were small, which resulted the lower values of the lower bound of 95% CI for some subgroup analyses. However, the point estimates were still high and consistent.

Table 8. Subgroup analyses by sex, age, race, and HCV genotypes, ITT

	Efficacy thresholds[a]	SVR12 Rate (n/N, Wilson Score 95% CI)	Clopper Pearson 95% CI
Sex			
Male	90.6%	96.9% (247/255, 95% CI: 93.9%, 98.4%)	95% CI: 93.9%, 98.6%
Female	89.7%	90.3% (28/31,95% CI: 75.1%, 96.7%)	95% CI: 74.2%, 98.0%
Age (years)			
<18	NA	NA (0/0, NA)	95% CI: NA
18 to <40	89.9%	94.5% (103/109, 95% CI: 88.5%, 97.5%)	95% CI: 88.4%, 98.0%
40 to <65	90.8%	96.9% (156/161, 95% CI: 92.9%, 98.7%)	95% CI: 92.9%, 99.0%
65 to <75	91.8%	100% (15/15, 95% CI: 79.6%, 100%)	95% CI: 78.2%, 100%
>=75	91.8%	100% (1/1, 95% CI: 20.7%, 100%)	95% CI: 2.5%, 100%
Race			
White	90.5%	95.5% (235/246, 95% CI: 92.2%, 97.5%)	95% CI: 92.1%, 97.7%
Black/African-American	91.2%	94.5% (30/30, 95% CI: 88.6%, 100%)	95% CI: 88.4%, 100%
Asian	89.2%	100% (7/7, 95% CI: 64.6%, 100%)	95% CI: 59.0%, 100%
Multiple	85.7%	100% (3/3, 95% CI: 43.9%, 100%)	95% CI: 29.2%, 100%
HCV Genotypes			
Genotype 1	90.7%	93.5% (159/165, 95% CI: 92.3%, 98.3%)	95% CI: 92.3%, 98.7%
Genotype 2	90.0%	100% (11/11, 95% CI: 74.1%, 100%)	95% CI: 71.5%, 100%
Genotype 3	89.0%	93.9% (31/33, 95% CI: 80.4%, 98.3%)	95% CI: 79.8%, 99.3%

Genotype 4	90.9%	97.9% (47/48, 95% CI: 89.1%, 99.6%)	95% CI: 88.9%, 99.9%

[a] Derived using PWID status classification 1.
Source: FDA reviewer. Produced using ADSL.xpt, ADEFFOUT.xpt

Table 9: Subgroup analyses by infection stage at baseline determined by HCV-specific virology and serology laboratory results alone, ITT

Infection stage at baseline	Criteria[a]	Efficacy thresholds[b]	SVR12 Rate (n/N, Wilson Score 95% CI)	Clopper Pearson 95% CI
Likely acute HCV	• Baseline HCV RNA ≥LLOQ, AND • Any HCV RNA <LLOQ between Day -210 and Baseline, OR negative HCV antibody between Day -150 and Baseline	89.9%	93.5% (58/62, 95% CI: 84.6%, 97.5%)	95% CI: 84.3%, 98.2%
Likely acute or early HCV	• Baseline HCV RNA ≥LLOQ • At least 1 HCV antibody negative or RNA <LLOQ result since Day -365 • Excluding Likely Acute HCV above	90%	100% (46/46, 95% CI: 92.3%, 100%)	95% CI: 92.3%, 100%
Spontaneous HCV clearance	• Baseline HCV RNA <LLOQ	91.8%	100% (12/12, 95% CI: 75.7%, 100%)	95% CI: 73.5%, 100%
Likely chronic HCV	• Baseline HCV RNA ≥LLOQ • No negative HCV antibody result • No pre-treatment HCV RNA <LLOQ • At least one HCV RNA ≥LLOQ on Day -181 or earlier	88.8%	100% (6/6, 95% CI: 61.0%, 100%)	95% CI: 54.1%, 100%
Unclear based on Virology/Serology Alone	• All other participants who did not meet any of the other criteria	90.8%	96% (153/160, 95% CI: 91.2%, 97.9%)	95% CI: 91.2%, 98.2%

[a]: Please see Clinical Virology Section 7.1 for their rationale of this classification.
[b]: Derived using PWID status classification 1.
Source: FDA reviewer. Produced using ADSL.xpt, ADEFFOUT.xpt

7. Clinical Virology

7.1 Exploratory Analyses of Acute HCV Status

As this was the first application for approval of a DAA regimen for the treatment of patients with acute HCV infection, a detailed investigation was conducted to understand the baseline disease characteristics of the M20-350 study population and confirm study participants truly represented a patient population with an acute HCV infection.

In simplest terms, acute HCV infection is typically defined as an infection that occurred within the previous 6 months, while chronic HCV infection is defined as an infection that has persisted for >6 months[21] . However, diagnosis of acute HCV infection can be challenging, as infected individuals may not have a discrete recognized HCV exposure or sufficient laboratory data to determine the precise timing of HCV infection. Therefore, a variety of factors, including specific and nonspecific laboratory testing and timing of known HCV-associated risk behaviors, are often considered in the diagnosis of acute HCV infection.

Current IDSA/AASLD treatment guidelines[17] include detailed guidance on diagnosis of acute HCV infection; see https://www.hcvguidelines.org/unique-populations/acute-infection, https://www.hcvguidelines.org/evaluate/testing-and-linkage, and references therein. Specific laboratory testing involved in the diagnosis of acute HCV infection may include analyses of blood samples for HCV RNA (quantitative or qualitative), HCV core antigen or anti-HCV antibody. Longitudinal laboratory results of negative detection of HCV RNA or core antigen, followed by a positive test result, all within a 6-month period, would strongly indicate acute HCV infection. In the absence of longitudinal virology results, the positive detection of HCV RNA or core antigen coupled with a negative test result for anti-HCV antibody at the same time is also strongly indicative of acute HCV infection (with possible exception of those with severe immune deficiency), as it would identify individuals with recent HCV infection who have not yet developed a detectable antibody response, which typically occurs 1-2 months after initial HCV exposure. Nevertheless, positive detection of anti-HCV antibody does not rule out acute HCV infection, as the acute infection period extends beyond the initial detection of anti-HCV antibody. Furthermore, individuals may have had a prior HCV infection that resolved from spontaneous or treatment-induced viral clearance, followed by a new HCV infection even in the presence of anti-HCV antibody from the prior infection. Fluctuating or low HCV RNA levels may also be indicative of acute HCV infection, as levels are generally more stable in the chronic period. Spontaneous HCV clearance is also more common in the acute HCV infection period.

In addition to HCV virology and serology laboratory findings, evidence of liver injury, such as elevated alanine aminotransferase (ALT), may also indicate acute HCV infection, particularly if the individual has known risk factors for recent HCV exposure. However, because this is a nonspecific marker, it is important to test for alternate or coexisting causes of acute hepatitis.

Table 10 (FDA analysis) summarizes the key M20-350 protocol inclusion criteria related to the diagnosis of acute HCV infection and includes a breakdown of numbers of participants who met each specific criterion.

Table 10: M20-350 inclusion criteria related to diagnosis of acute HCV infection.
The 4 sub-criteria were not mutually exclusive.

Acute HCV-Related Inclusion Criteria	% (n/N) Participants Meeting Criterion
Physician diagnosis of acute HCV infection, quantifiable HCV RNA at Screening, and at least 1 of the following:	
1) Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; OR	29% (83/286)
2) Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen; OR	31% (90/286)
3) Clinical signs and symptoms compatible with acute hepatitis (ALT >5× upper limit of normal [ULN] and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen; OR	84% (239/286)
4) Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening.	15% (43/286)

Source: FDA reviewer. Produced using ADSL.xpt.

These acute HCV-related inclusion criteria were previously agreed upon with the sponsor at the time of M20-350 protocol review, are consistent with the CDC case definition for acute HCV infection, and reasonably reflect how acute HCV infection may be diagnosed in clinical practice. Nevertheless, the criteria are broader than the strict definition of acute HCV infection (i.e., infection duration <6 months), allowing for possible inclusion of participants who are not truly in the acute infection phase. For example, in some cases the windows for laboratory-based criteria extend beyond the 6 months prior to Screening. Also, the documentation of risk behaviors for HCV infection within the prior 6 months does not exclude the possibility that such risk behaviors also occurred earlier and resulted in HCV infection >6 months prior to Screening. Furthermore, all of these criteria were assessed at the Screening visit(s), and with a period of up to ~1 month between screening and treatment initiation (i.e., baseline), it is possible for participants' HCV infection status to change prior to treatment initiation, including transition from acute to chronic HCV infection or spontaneous clearance of the infection. Only 15% of participants met the most stringent criterion (#4) based on HCV serology and virology testing within the 5 months prior to Screening, and only 9 (3%) participants had a negative anti-HCV antibody test result at baseline or other latest available pre-treatment timepoint.

Exploratory analyses were conducted to understand in greater detail participants' HCV infection status at baseline (i.e., treatment start) according to HCV-specific virology and serology laboratory results. Based on these laboratory results and their timing, participants were grouped into one of five different baseline HCV disease statuses, as defined in **Table 11**.

These analyses considered both the central laboratory data (LB dataset) as well as other local microbiology laboratory data (MB dataset) in the trial record.

Table 11. Exploratory categorization of baseline HCV infection status based on HCV-specific virology and serology laboratory results.

HCV Infection Status at Baseline	Definition
Likely Acute HCV	• Baseline HCV RNA ≥LLOQ, AND • Any HCV RNA <LLOQ between Day -210 and Baseline, OR negative HCV antibody between Day -150 and Baseline
Likely Acute or Early HCV	• Baseline HCV RNA ≥LLOQ • At least 1 HCV antibody negative or RNA <LLOQ result since Day -365 • Excluding Likely Acute HCV above
Spontaneous HCV Clearance	• Baseline HCV RNA <LLOQ
Likely Chronic HCV	• Baseline HCV RNA ≥LLOQ • No negative HCV antibody result • No pre-treatment HCV RNA <LLOQ • At least one HCV RNA ≥LLOQ on Day -181 or earlier
Unclear Based on Virology/Serology Alone	• All other participants who did not meet any of the other criteria

Source: FDA reviewer.

Table 12 (FDA analysis) shows the proportion of participants in each of these baseline HCV disease status groups based on HCV-specific virology and serology laboratory results. **Table 12** also includes a breakdown of the acute HCV-related protocol inclusion criteria met for each group, plus the SVR12 rate for each group.

Table 12. Proportions of participants in each baseline HCV infection status based on HCV-specific virology and serology laboratory results.

HCV Infection Status at Baseline	% (n/N)	% Meeting Protocol Incl. Criteria (1/2/3/4)*	SVR12 Rate^
Likely Acute HCV	22% (62/286)	(76%/69%/71%/63%)	94% (58/62)
Likely Acute or Early HCV	16% (46/286)	(67%/91%/52%/4%)	100% (46/46)
Spontaneous HCV Clearance	4% (12/286)	(33%/33%/83%/17%)	100% (12/12)
Likely Chronic HCV	2% (6/286)	(0%/0%/100%/0%)	100% (6/6)
Unclear Based on Virology/Serology Alone	56% (160/286)	(1%/1%/97%/0%)	96% (153/160)

*M20-350 protocol inclusion criteria related to acute HCV infection:
1. Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening
2. Negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
3. Clinical signs and symptoms compatible with acute hepatitis (ALT > 5 × ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to Screening; AND risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
4. Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to Screening

^Intent-to-treat SVR12 rate. There were no cases of virologic failure (relapse or breakthrough).

Source: FDA reviewer: Produced using ADSL.xpt, LB.xpt, and MB.xpt

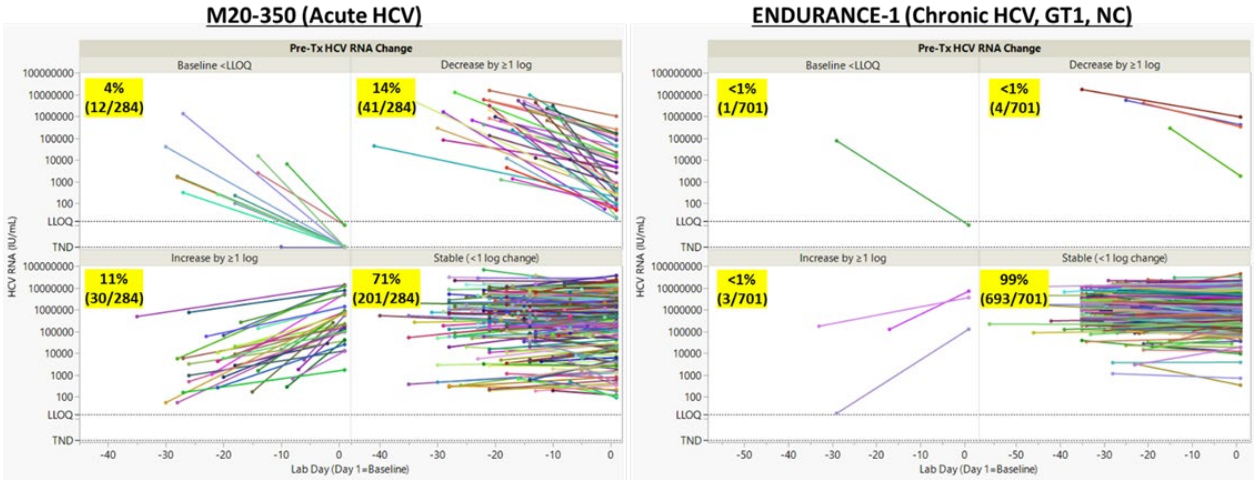
Approximately 22% of participants could be identified as being in the "Likely Acute HCV" infection phase at baseline, with virology and/or serology laboratory data indicating a new HCV infection within ~6 months of initiating treatment in M20-350. Another 16% of participants were classified as being in the "Likely Acute or Early HCV" infection phase, with laboratory evidence of new HCV infection within 1 year of initiating treatment in M20-350. Participants in this group could have been in the acute HCV phase but without sufficient HCV virology or serology laboratory results to distinguish between acute HCV infection (i.e., <6 months) and early chronic HCV infection (i.e., 6-12 months). Overall, among the 95% (272/286) of participants with HCV RNA ≥LLOQ at baseline (remaining 12 <LLOQ, and 2 w/missing data), 40% (108/272) had a documented result of negative HCV antibody or unquantifiable HCV RNA within the previous year, pooling the "Likely Acute HCV" and "Likely Acute or Early HCV" groups.

Approximately 4% of participants had evidence of spontaneous HCV clearance between Screening and treatment initiation, based on having HCV RNA <LLOQ at baseline. These participants likely did not require GLE/PIB treatment, or they could have delayed treatment to assess if HCV RNA levels remained durably <LLOQ without treatment. A small proportion of participants (2%) were likely in the chronic HCV infection period based on evidence of HCV RNA ≥LLOQ at least 6 months prior to baseline and with no negative anti-HCV antibody or pre-treatment HCV RNA <LLOQ results in the trial record.

The remainder of participants (56%) were in the "Unclear" group as they had insufficient HCV virology or serology laboratory data to conclusively determine their HCV infection status at baseline. The presence of acute HCV infection cannot be ruled out in this group. Rather, these participants were diagnosed with acute HCV infection based on other criteria, including nonspecific liver disease signs and having recent histories of risk behaviors for HCV infection. Not surprisingly, 97% of these participants (as well as 100% of participants in the "Likely Chronic HCV" group), met the least stringent acute HCV-related inclusion criterion (#3), which did not require any documented laboratory results of negative anti-HCV antibody or HCV RNA <LLOQ.

High efficacy of GLE/PIB was confirmed regardless of baseline HCV infection status, with all groups having an ITT SVR12 rate ≥94% and no cases of virologic failure (**Table 12**, FDA analysis).

As further evidence that the M20-350 study population was comprised primarily of those with acute HCV infection, participants' HCV RNA levels in the pre-treatment period between Screening and Baseline visits were more variable and dynamic compared to those observed in a previous GLE/PIB clinical trial, ENDURANCE-1, which included a chronic HCV infected population (**Figure 3**; FDA analysis). In addition to the ~4% of M20-350 participants who appeared to spontaneously clear their HCV infection in the pre-treatment period ("Baseline <LLOQ" group), 25% had a ≥1 $\log_{10}$ IU/mL increase (14%) or decrease (11%) in HCV RNA during this period. In contrast, only 1% of participants in ENDURANCE-1 had a similar change in HCV RNA levels during the pre-treatment period. Furthermore, among the remaining participants with relatively stable HCV RNA levels during the pre-treatment period (<1 $\log_{10}$ IU/mL change), levels were more widely distributed in the M20-350 population compared to the ENDURANCE-1 population.



Source: FDA reviewer. Produced using ADSL.xpt and LB.xpt; plus ADSL.xpt and LB.xpt from ENDURANCE-1

Figure 3. Analysis of HCV RNA levels in the pre-treatment period in M20-350 and a comparator trial that enrolled noncirrhotic (NC), HCV GT1 chronically infected participants (ENDURANCE-1). Colored lines illustrate HCV RNA levels for individual participants between Screening and Baseline timepoints. Screening sample timepoints considered in this analysis were restricted to those within 60 days of Baseline, and the earliest

result was considered for participants with ≥2 Screening results in this time range. Note that ENDURANCE-1 required participants to have HCV RNA >10^3 IU/mL at Screening, which may have caused some bias in the analysis, although this likely had little impact considering >99% of participants in ENDURANCE-1 had HCV RNA >10^4 IU/mL, and 96% had HCV RNA >10^5 IU/mL.

7.2 HCV Genotypes/Subtypes

Baseline HCV genotypes and subtypes, both overall and grouped by study site country, are summarized in **Table 13** (FDA analysis).

Table 13. Summary of participants' HCV genotypes/subtypes at baseline. Results are based on HCV phylogenetic analysis, or from the clinical assay (line probe assay [LiPA]) if phylogenetic results were not available.

HCV Genotype Overall (n=286)			HCV Subtype Overall (n=286)			HCV Subtype Breakdown by Country															
						U.S.		Australia		Austria		Canada		France		Germany		Italy		Spain	
	N	%		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	165	57.7%	**1a**	156	54.5%	37	54.4%	1	50.0%	3	42.9%	6	46.2%	6	33.3%	41	56.9%	6	35.3%	56	62.9%
			1b	9	3.1%	3	4.4%	0		2	28.6%	0		0		3	4.2%	0		1	1.1%
2	11	3.8%	**2-und.**	2	0.7%	0		0		0		0		0		0		0		2	2.2%
			2b	7	2.4%	5	7.4%	0		0		1	7.7%	0		0		1	5.9%	0	
			2c	2	0.7%	0		0		0		0		0		0		0		2	2.2%
3	33	11.5%	**3-und.**	1	0.3%	1	1.5%	0		0		0		0		0		0		0	
			3a	32	11.2%	14	20.6%	0		1	14.3%	3	23.1%	1	5.6%	7	9.7%	4	23.5%	2	2.2%
4	48	16.8%	**4-und.**	14	4.9%	0		0		0		1	7.7%	2	11.1%	4	5.6%	1	5.9%	6	6.7%
			4d	34	11.9%	0		0		0		0		4	22.2%	13	18.1%	3	17.6%	14	15.7%
Unk.	29	10.1%	**Unk.**	29	10.1%	8	11.8%	1	50.0%	1	14.3%	2	15.4%	5	27.8%	4	5.6%	2	11.8%	6	6.7%

und., subtype undetermined; unk., genotype and subtype unknown
Source: FDA reviewer. Produced using ADSL.xpt, AXPHYLO.xpt, LB.xpt, and ADEFFOUT.xpt

7.3 Participants with SVR12 Failure

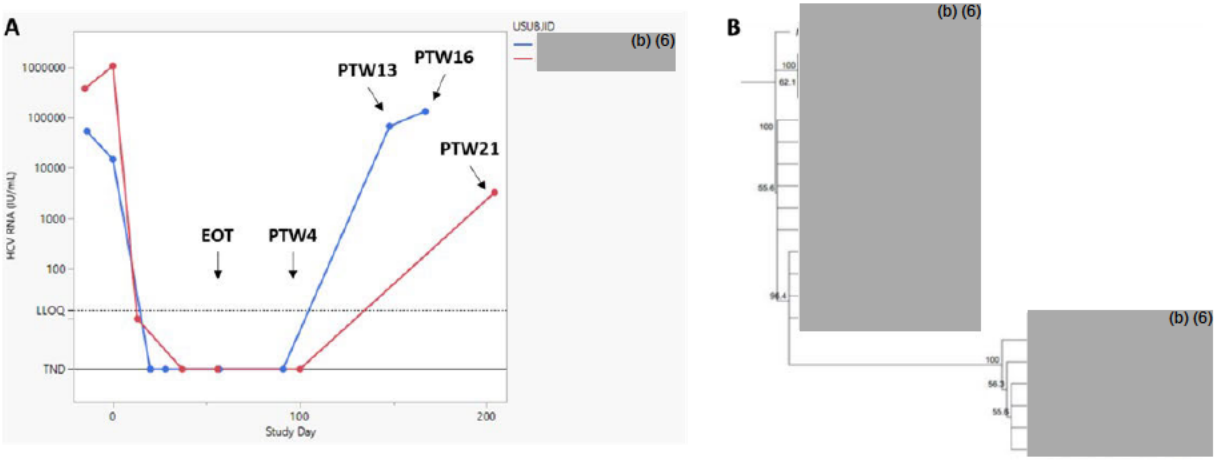
A total of 11 participants did not achieve SVR12 (ITT). The sponsor's classification of nonresponse reason and last available HCV RNA results for each non-SVR12 participant are shown in **Table 14** (FDA analysis). None of the 11 participants experienced protocol-defined virologic failure, which could have included on-treatment virologic failure or post-treatment relapse. Nine participants did not achieve SVR12 due to "Discontinuation of Treatment" or "Missing SVR12 Data," and of these, 7 participants had HCV RNA <LLOQ/Not Detected at the last available timepoint, and the other 2 participants only had available HCV RNA results on Day 1 or Day 21.

Table 14. Individual participants who did not achieve SVR12.

USUBJID	Baseline HCV Subtype	Nonresponse Reason (Acc. to Sponsor)	Latest HCV RNA Result (Study Day)	Days Post-Tx	Weeks Post-Tx	HCV RNA (IU/mL)
(b) (6)	3a	DISCONTINUATION OF TREATMENT	1	0	0	23
	Unknown	DISCONTINUATION OF TREATMENT	17	0	0	NOT DETECTED
	4d	DISCONTINUATION OF TREATMENT	21	0	0	22*
	3a	MISSING SVR12 DATA	29	0	0	NOT DETECTED
	1b	DISCONTINUATION OF TREATMENT	36	0	0	NOT DETECTED
	1a	DISCONTINUATION OF TREATMENT	54	7	1	NOT DETECTED
	1a	MISSING SVR12 DATA	84	27	4	NOT DETECTED
	Unknown	MISSING SVR12 DATA	85	29	4	NOT DETECTED
	1a	MISSING SVR12 DATA	113	54	8	NOT DETECTED
	1a	REINFECTION	168	110	16	132000
	1a	REINFECTION	205	148	21	3210

*Participant's HCV RNA level at baseline was 177,000 IU/mL.
Source: FDA reviewer. Produced by using LB.xpt, ADSL.xpt, and ADEFFOUT.xpt

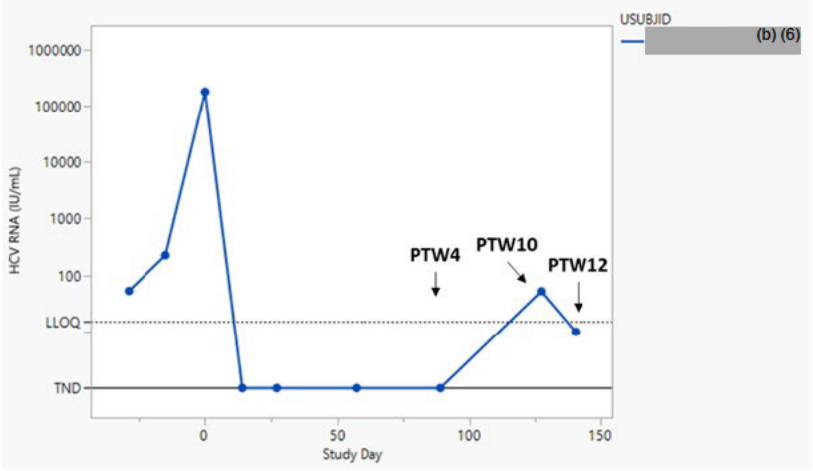
Two of the non-SVR12 participants had clear post-treatment rebounds in viral RNA levels (**Figure 4;** FDA analysis and SDN 1292 sponsor response document, pg. 5). The sponsor considered both participants as having failed to achieve SVR12 due to reinfection, and not due to virologic relapse, because in both participants the HCV populations in the post-treatment period differed genetically from their respective baseline HCV populations, which could indicate a new HCV infection. Participant (b) (6) had the same HCV genotype/subtype (GT1a) detected at baseline and in the post-treatment period; however, the baseline and post-treatment viral sequences did not cluster together phylogenetically. Participant (b) (6) had a switch in their HCV genotype/subtype from GT1a at baseline to GT3a in the post-treatment period. Consistent with the HCV reinfection determination, both participants had documented risk behaviors for HCV reinfection in the post-treatment period, including engaging in unprotected sexual activity with multiple partners or sharing drug injection equipment (CSR Appendix 16.2_6.1.6).



Sources: (A) FDA reviewer. Produced using LB.xpt and ADSL.xpt; (B) Applicant, SDN 1292 sponsor response document

Figure 4. (A) HCV RNA levels and (B) phylogenetic analysis of Baseline visit (D1) and Post-Treatment Week 12 (PTW12) visit HCV NS5A sequences for two participants who were classified as having HCV reinfection in the post-treatment period. In (B), the noted PTW12 visits for Participants (b) (6) (indicated in bold) correspond to actual Day 149 (PTW13) and Day 205 (PTW21), respectively, as shown in (A). Phylogenetic analysis of the HCV NS3/4A region showed similar results as (data not shown). Abbreviations: EOT, end-of-treatment; LLOQ, lower limit of quantification (imputed as 15 IU/mL); TND, target not detected (imputed as 1 IU/mL)

One participant (b) (6) who achieved SVR12 based on the definition of HCV RNA <LLOQ at PTW12 had an unusual transient result of HCV RNA ≥LLOQ earlier in the post-treatment period (**Figure 5**; FDA analysis). Also, the viral RNA result at the PTW12 visit was <LLOQ/Detected. In contrast, the other 274 participants who achieved SVR12 altogether had 683 HCV RNA results in the post-treatment period, of which 676 (99%) were reported as <LLOQ/Not Detected. Typically, HCV relapse following DAA treatment is associated with HCV RNA levels several orders of magnitude above the assay LLOQ[22], so the PTW12 <LLOQ/Detected result likely reflects a true SVR with detection of a low, clinically insignificant level of HCV RNA. Another possible explanation for this HCV RNA pattern is the participant was re-infected with HCV in the post-treatment period and the infection was in the process of being cleared by the participant's immune response. Ideally, later follow-up results would have been available to confirm durability of virologic suppression beyond PTW12. We inquired with the sponsor if any such data were available, and the sponsor replied that no further data are available as such testing would fall outside the parameters of the protocol and consent.



Source: FDA reviewer. Produced using LB.xpt and ADSL.xpt

Figure 5. HCV RNA results for Participant (b) (6), who achieved SVR12 after a transient post-treatment HCV RNA result ≥LLOQ.

7.4 GLE/PIB Resistance

Baseline HCV sequencing results were obtained from 65% (186/286) of participants. Based on previous nonclinical and clinical resistance analyses, and consistent with similar analyses described in the MAVYRET® label, the following NS3 and NS5A amino acid positions are considered "signature" resistance-associated positions for GLE and PIB, respectively:

- NS3 positions: 155, 156, and 168
- NS5A positions: 24, 28, 30, 31, 58, 92, and 93

From this list of "signature" positions, 25% (47/186) of participants had virus with ≥1 GLE or PIB resistance-associated polymorphism (RAP), including <1% (1/170) with an NS3 RAP and 25% (46/181) with an NS5A RAP; denominators are based on numbers of participants with available sequencing data for the noted target. **Table 15** (FDA) analysis lists all of the GLE or PIB RAPs that were detected.

Table 15. Baseline HCV GLE (NS3) and PIB (NSA) resistance-associated polymorphisms (RAPs) detected in study participants at ≥15% NGS sensitivity cutoff. RAPs included any change at NS3 position 155, 156, or 168, or NS5A position 24, 28, 30, 31, 58, 92, or 93.
*Percentages based on numbers of participants within indicated HCV subtype (or overall for "Any") with available sequencing data.

HCV Subtype	Polymorphism	N (%)*
NS3 RAPs (n=170 all GTs)	**Any**	**1 (<1%)**
GT3a (n=20)	R155K	1 (5%)
NS5A RAPs (n=181 all GTs)	**Any**	**46 (25%)**
GT1a (n=118)	K24E	1 (1%)
	K24Q	1 (1%)

	M28V	14 (12%)
	Q30R	3 (3%)
	H58C	1 (1%)
	H58P	2 (2%)
	H58R	1 (1%)
	Y93C	1 (1%)
GT1b (n=7)	P58L	1 (14%)
GT2b (n=3)	M31L	2 (67%)
GT2c (n=2)	R30K	2 (100%)
GT3a (n=21)	A30K	1 (5%)
	A30T	1 (5%)
	P58L	1 (5%)
GT4d (n=30)	T58L	2 (7%)
	T58P	16 (53%)
	T58S	1 (3%)

Source: FDA reviewer. Produced using AXRS.xpt, ADEFFOUT.xpt, AXPHYLO.xpt, and LB.xpt.

Baseline HCV GLE or PIB RAPs were not associated with virologic failure, as all 47 participants with baseline RAPs achieved SVR12.

Neither of the two participants with presumed HCV reinfection (b) (6) had an HCV GLE or PIB signature RAP detected at baseline. Participant (b) (6) who had an HCV genotype switch from GT1a at baseline to GT3a in the post-treatment period, had an NS5A A30K potential RAP detected in the post-treatment virus. Participant (b) (6) who had a GT1a clade switch from baseline, had no RAPs detected in the post-treatment virus.

8. Safety

This section presents a summary of the clinical reviewer's analyses of safety data generated from Study M20-350, a Phase 3b, multicenter, single-arm, prospective study designed to evaluate the safety and efficacy of 8 weeks of GLE/PIB treatment in adult and adolescent participants ≥ 12 years of age with physician-diagnosed acute HCV infection.

8.1 Methods

Safety data for the sNDAs (NDA 209394 S-19 and NDA 215110 S-05) were submitted by the Applicant as a Clinical Study Report (CSR), Clinical Summary, and electronic datasets.

Treatment-emergent events were defined as any adverse events (AEs) with onset dates on or after study drug start date and no later than 30 days after permanent study drug discontinuation, as well as any AEs leading to premature discontinuation of study drug. The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (published June 14, 2010) was used for grading of AEs and laboratory abnormalities.

The following AEs were considered Adverse Events of Special Interest (AESI):

- Treatment-emergent hepatic decompensation/hepatic failure events, identified using the AbbVie PMQ for hepatic decompensation and hepatic failure
- Postbaseline treatment-emergent and non-treatment-emergent events of HCC identified with the MedDRA PTs of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent.

Safety data was reported according to MedDRA version 27.0. The FDA data analyses were performed using JMP Clinical data analysis tools. The safety analysis set, which included all 286 participants enrolled in Study 20-350, was used for all analyses. Even in cases where Applicant tables are displayed, data were verified by the Clinical Reviewer.

8.2 Exposure

All participants enrolled in Study M20-350 were to receive GLE/PIB (300 mg/120 mg) for 8 weeks (56 days). A total of 286 participants took at least one dose and were included in the safety analysis. Two hundred and sixty-three (263, 92.0%) participants completed the full GLE/PIB treatment course. The mean treatment duration was 56.6 days with a standard deviation of 5.62 days, while the median duration was 57.0 days.

8.3 Overview of Treatment-Emergent AEs

An overview of AEs reported during Study M20-350 is show in **Table 16** below. The frequency of reported events is similar to that observed in the clinical trials conducted to support the original GLE/PIB NDA approval (for the treatment of chronic HCV infection indication) (b) (4)

Table 16. Overview of Treatment Emergent AEs (Study M20-350)

Event	Percent of participants (n)
Any AE	59.8 % (171)
Treatment-Related AE	15.7% (45)
Any AE Grade ≥ 3 in Severity	5.6% (16)
Treatment-Related AE Grade ≥ 3	0
Any SAE	3.5% (10)
Any Treatment-Related SAE	0
AE Leading to Permanent Discontinuation of GLE/PIB	0.3% (1)
Death	0

Source: FDA analysis; ADSL and ADAE

8.4 Deaths

No participants died during the study.

8.5 Serious Adverse Events

Ten participants (3.5%) experienced a total of 19 treatment emergent SAEs; the events are shown by Body System or Organ Class and Lowest Level Terms in **Table 17**. Except for limb abscess, which affected two participants, each reported SAE occurred in a single study participant. There were no SAEs related to hepatoxicity or hepatic decompensation. None of the SAEs resulted in discontinuation of treatment.

None of the SAEs were attributed to the study treatment. The Clinical Reviewer conducted a review of each of the SAE narratives and agreed with the Applicant that the SAEs are likely unrelated to treatment. The Clinical Reviewer determined that the SAEs were most likely attributable to accidents and comorbidities, particularly opioid use disorder. Of note, although the MAVYRET label describes a potential risk of hypoglycemia due to changes in hepatic function following successful treatment of HCV infection with direct-acting antivirals, the Clinical Reviewer agrees with the Applicant that the SAE of hypoglycemia in this study is unrelated to study drug; this hypoglycemia event is likely related instead to decreased oral intake and sepsis, as it occurred in the context of a hospitalization for MRSA bacteremia and peri-orbital cellulitis, which were also reported as unrelated SAEs.

Table 17. SAEs by Body System Organ Class (Study M20-350)

SAE Body System Organ Class/Lowest Level Term	Number of Events
Infections and infestations	**6**
Abscess of finger	1
Bacteremia	1
Methicillin-resistant Staphylococcus aureus infection	1
Periorbital cellulitis	1
Septic emboli	1
Thigh abscess	1
Gastrointestinal disorders	**2**
Acute enterocolitis	1
Rectal perforation	1
Psychiatric disorders	**2**
Drug abuse	1
Substance-induced psychotic disorder	1
Injury, poisoning and procedural complications	**7**
Alcohol poisoning	1
Broken ankle	1
Drug overdose	1
Drug poisoning	1
Fractured ribs	1
Illicit drug intoxication	1
Road traffic accident	1
Metabolism and nutrition disorders	**1**
Hypoglycemia	1

Reproductive system and breast disorders	**1**
Pain pelvic	1
Total SAEs	**19**

Source: FDA analysis; ADSL and ADAE

8.6 Grade 3 or higher AEs

As shown in **Table 18** below, 16 (5.6%) participants experienced at total of 25 AEs of Grade 3 severity or higher. Most Grade 3 or higher AEs were also reported as SAEs and are discussed in **Section 8.4**. None of these Grade 3 or higher AEs were attributed to the study treatment. FDA analysis of the data revealed no discernible patterns in either the nature or frequency of Grade 3 or higher AEs other than their relation to the underlying comorbidities in the study population.

Table 18. Grade 3 or Higher AEs (Study M20-350)

Grade 3 or 4 AE, Preferred Term	Number of Participants (Percent)
Any adverse event	16 (5.6)
Abscess limb	2 (0.7)
Alcohol poisoning	1 (0.3)
Ankle fracture	1 (0.3)
Bacteremia	1 (0.3)
Blood potassium decreased	1 (0.3)
Drug abuse	1 (0.3)
Enterocolitis	1 (0.3)
Hypoglycemia	1 (0.3)
Infection	1 (0.3)
Joint dislocation	1 (0.3)
Lymphogranuloma venereum	1 (0.3)
Myopia	1 (0.3)
Otitis media acute	1 (0.3)
Overdose	1 (0.3)
Pelvic pain	1 (0.3)
Periorbital cellulitis	1 (0.3)
Rectal perforation	1 (0.3)
Rib fracture	1 (0.3)
Road traffic accident	1 (0.3)
Septic embolus	1 (0.3)
Staphylococcal infection	1 (0.3)
Substance-induced psychotic disorder	1 (0.3)
Toxicity to various agents	1 (0.3)
Treponema test positive	1 (0.3)

Source: Applicant; CSR Table 14.3_1.4.2

8.7 Common AEs and Reactions

As shown in **Table 19** below, 171 (59.8%) participants experienced at least one AE during the study period. The most frequently reported AEs were diarrhea (6.3%), fatigue (6.3%), and nasopharyngitis (4.9%). AEs related to study treatment (adverse drug reactions) that occurred in ≥ 1% of participants were fatigue in 10 participants (3.5%), asthenia and headache in 7 participants each (2.4%), diarrhea in 5 participants (1.7%), and nausea in 4 participants (1.4%).

The frequency and nature of reported AEs and adverse reactions is similar to those observed in the clinical trials conducted to support the original GLE/PIB NDA.

Table 19. AEs Reported for ≥ 2% of Participants (Study M20-350)

Preferred Term	Number (%) of Subjects (N = 286)
Any AE	171 (59.8)
Diarrhoea	18 (6.3)
Fatigue	18 (6.3)
Nasopharyngitis	14 (4.9)
Headache	12 (4.2)
Asthenia	10 (3.5)
COVID-19	9 (3.1)
Nausea	8 (2.8)
Gonorrhoea	7 (2.4)
Anal gonococcal infection	6 (2.1)

Cross reference: Table 14.3__1.2.2.1

Source: Applicant; CSR Table 16

8.9 Discontinuations for AEs and Reactions

One participant (b) (6) discontinued treatment due to AE. The participant, a 23-year-old man with a congenital urethral deformation, kidney stones and recently placed ureteral stent experienced a Grade 2 AE of gastric pain (preferred term "abdominal pain upper") on day 52 of treatment. The AE was not reported as an SAE or considered related to study treatment. The participant was diagnosed with acute HCV and had significant hyperbilirubinemia (46 umol/L; approximately 2XULN) and ALT elevation (60 U/L; ULN 48) at baseline prior to treatment. His ALT declined on treatment and normalized by end of treatment. He experienced a slight transient increase in bilirubin on treatment (to 75 umol/L approximately 3X ULN at day 29, which subsequently declined but remained above the limit of normal at day 90 (36 umol L, ULN 21 umol/L). He also experienced the adverse events of jaundice, eructation, urinary tract infection, and hypovitaminosis on treatment. The participant achieved SVR12. The event is

listed as ongoing and continuous and may be related to the participant's pre-existing urinary tract issues and urinary tract infection, but this was not explicitly stated in the narrative.

An addition three participants (1.0%) experienced at least one AE resulting in the temporary interruption of study treatment. One participant (b) (6) reported Grade 1 AEs, including diarrhea, nausea, and regurgitation, which were deemed potentially related to the study treatment. The other two participants (b) (6) experienced SAEs (finger/limb abscess and overdose, respectively) that led to treatment interruption but were not considered related to the study treatment. All events were resolved, allowing for the resumption of study treatment. Two of three of these participants achieved SVR12. Participant (b) (6) had missing SVR12 data.

8.10 Vital Signs

No clinically significant trends in vital signs were observed. No clear signal of vital sign abnormalities has been observed in prior studies of MAVYRET.

8.11 Pregnancy

Women who were pregnant or lactating were excluded from Study M20-350. Any woman who became pregnant while on study treatment was to be withdrawn from the study.

One participant reported an ectopic pregnancy as an AE, no other pregnancies were reported. No new information regarding use in pregnancy and lactation was provided by results from Study M20-350.No adequate human data are available to establish whether or not MAVYRET poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when the components of MAVYRET were administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) the human exposures at the recommended dose of MAVYRET.

The background risk of major birth defects and miscarriage for the indicated population (acute hepatitis C) is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.12 Laboratory Abnormalities

Given that previous clinical trials have thoroughly evaluated the safety of GLE/PIB and identified no significant laboratory abnormalities beyond elevated serum bilirubin levels, Study M20-350 was designed to focus on the following laboratory-related liver safety endpoints:

- ALT elevations of NCI CTCAE Version 4.03 Grade 1, 2, 3, or 4 during the Treatment Period with ALT grade increased from Baseline.
- Post-nadir ALT elevation > 3 × ULN with total bilirubin > 2 × ULN during the Treatment Period.

When considering the Sponsor's proposal to evaluate GLE/PIB treatment for the treatment of acute HCV infection, the Clinical Reviewer's primary safety concern was liver toxicity. Specifically, the reviewer was concerned that people with acute HCV infection might be more susceptible to liver injury than those with chronic HCV infection. Consequently, the FDA agreed with the Sponsor's proposal to focus on liver-related laboratory safety endpoints.

Despite the focus on liver-related safety, routine safety laboratory tests (hematology, clinical chemistries, urinalysis, and coagulation tests) were performed for all participants during all study visits. Results of these laboratory safety tests were reviewed by the Clinical Reviewer. No safety signals were observed in the review of safety laboratory tests.

The remainder of this section of the will focus on liver-related laboratory safety endpoints.

Treatment-Emergent Graded Elevations in ALT and Bilirubin

Abnormalities in ALT and bilirubin were similar in pattern to those seen in the original NDA 209394 submission review. **Table 20** shows baseline ALT and bilirubin toxicity grades and maximum on-treatment toxicity grades that worsened from Baseline among those with samples available at both timepoints (282/286 participants).

As shown in **Table 20**, most study participants had graded ALT elevations at Baseline, including 83 (29%) who had Grade 3 or higher ALT elevations. Only 3 participants (1.1%) experienced on-treatment ALT elevations that worsened in grade from baseline; all were transient and maximum Grade 1(**Table 20**).

Thirty-four (12.1%) participants had graded elevations in bilirubin at Baseline, including 3 (1.1%) who had Grade 3 bilirubin elevations (**Table 20**). On-treatment bilirubin increases that worsened in grade from Baseline were not uncommon in the study; 24 participants (8.5%) developed Grade 1 post-baseline maximum toxicity grades for bilirubin, 14 (5%) developed Grade 2 post baseline maximum toxicity grades and 1 participant (0.4%), developed a Grade 3 post-baseline bilirubin max toxicity grade elevation of bilirubin (**Table 20**). Bilirubin increases were transient and were not associated with ALT elevations or hepatic decompensation. MAVYRET inhibits OATP1B1/3 and is a weak inhibitor of UGT1A1 and may have the potential to impact bilirubin transport and metabolism, including direct and indirect bilirubin.

Table 20: Baseline Toxicity Grades and Maximum On-Treatment Toxicity Grades that Worsened from Baseline Grade for ALT and Total Bilirubin (Study M20-350)

	n/N Observed (%) (N = 286)	
Maximum Toxicity Grade[a,b]	**Baseline**	**Post-Baseline[c]**
ALT		
Grade 1	80/282 (28.4)	3/282 (1.1)
Grade 2	57/282 (20.2)	0/282

Grade 3	75/282 (26.6)	0/282
Grade 4	8/282 (2.8)	0/282
Total bilirubin		
Grade 1	19/282 (6.7)	24/282 (8.5)
Grade 2	12/282 (4.3)	14/282 (5.0)
Grade 3	3/282 (1.1)	1/282 (0.4)
Grade 4	0/282	0/282

a. Grades based on NCI CTCAE Version 4.03.

b. Participant must have had a baseline and at least 1 postbaseline value during treatment for the respective parameter to be included in the summary.

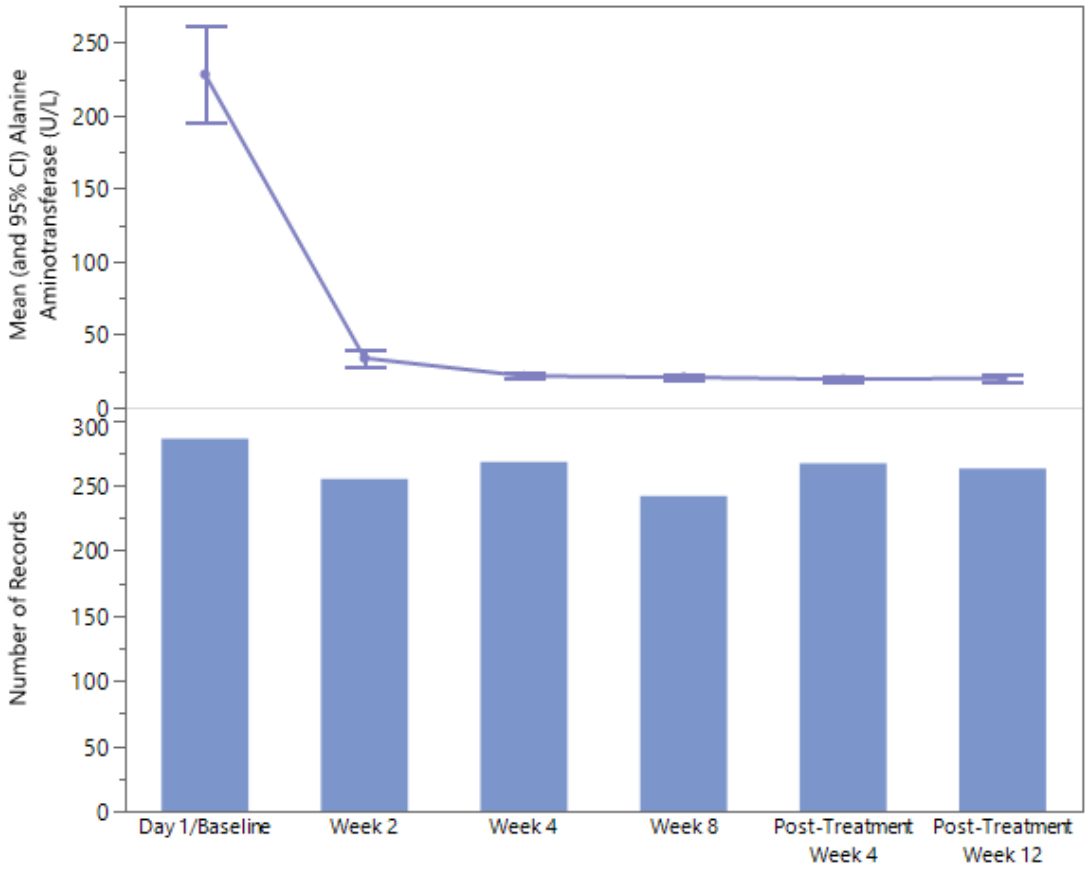
c. Grade must have been moreextreme than baseline grade. Cross reference: Table 14.3 _____4.4.1.1

Source: Applicant CSR Table 18.

Changes in ALT On-Treatment and Post-Treatment

As shown in **Figure 6**, mean ALT values decreased to within the normal range on-treatment by Week 2 and remained within the normal range throughout the study including during the post-treatment follow-up period.

Figure 6: Mean Observed ALT by Study Visit (Study M20-350)



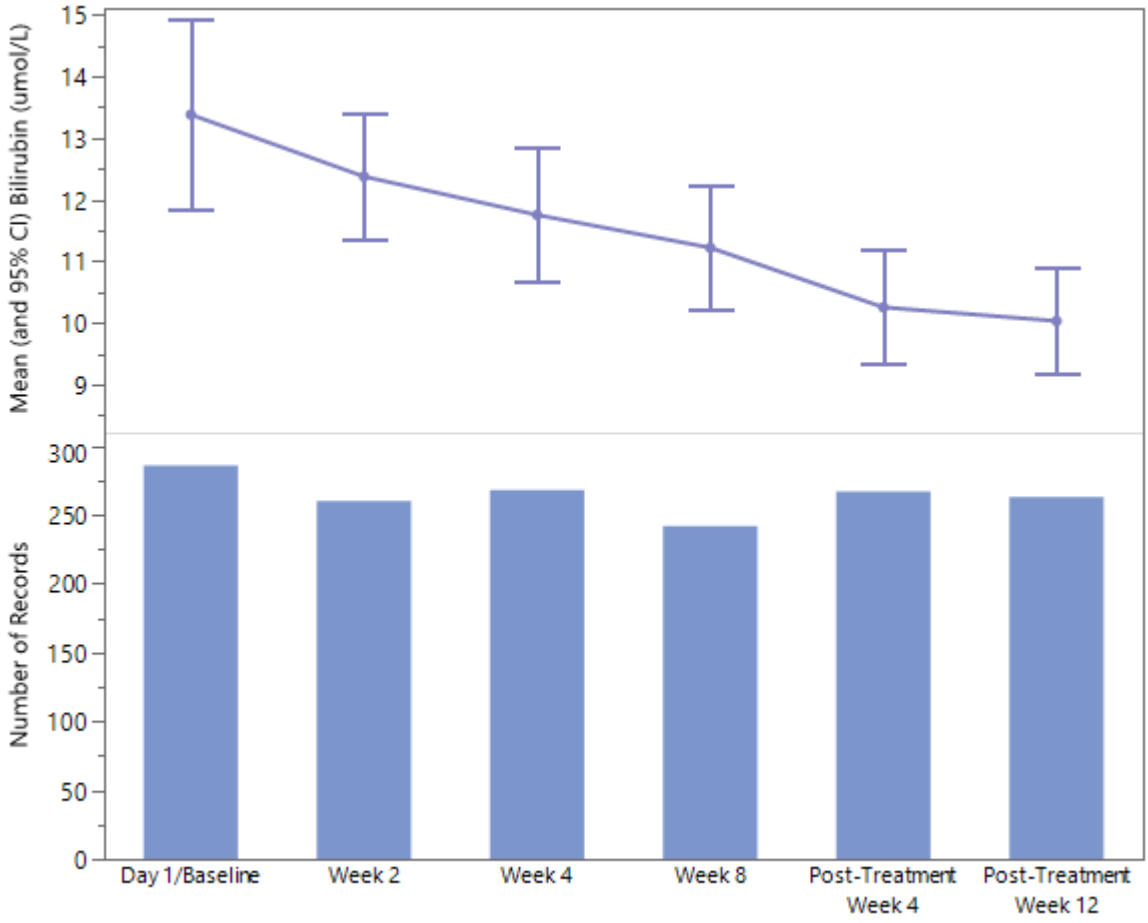
Source: FDA reviewer. Produced using ADLB.

Improvements in ALT values were also seen on the individual participant level. All but one participant experienced significant decreases in ALT from baseline on treatment and through the last available data point. The participant who was the exception had a diagnosis of acute hepatic failure, endocarditis, splenic rupture, and portal vein thrombosis at Baseline preceding treatment. After a single dose of study treatment, he was lost to follow-up for approximately 9 months. His final ALT during this follow-up visit was higher than this baseline ALT but similar to his original screening ALT value. All other participants with baseline ALT elevations of Grade 2, 3, or 4 improved from Baseline to a lesser grade at Week 4 (55, 73, and 6 participants, respectively) and at the final treatment visit (57, 75, and 8 participants, respectively).

Changes in Bilirubin On-Treatment and Post-Treatment

As shown in **Figure 7**, mean total bilirubin values decreased during treatment and at Post-Treatment Visit Weeks 4 and 12.

Figure 7: Mean Change in Bilirubin by Study Visit (Study M20-350)



Source: FDA reviewer. Produced using ADLB.

Overall downward trends in total bilirubin levels are also observed when evaluating graded bilirubin elevations of individual participants over time on study. Of the participants who had Grade 2 total bilirubin elevations at Baseline, 9 participants (75.0%) and 8 participants (66.7%) improved from baseline to a lesser grade at Week 4 and at the final treatment visit, respectively. Similarly, of the participants who had Grade 3 total bilirubin elevations at Baseline, all improved from Baseline at Week 4 and at the final treatment visit. No participant had a baseline total bilirubin elevation of Grade 4.

No participants discontinued or interrupted treatment due to bilirubin increase. One participant (0.3%) experienced transient jaundice on treatment. No participant developed liver decompensation. By the end of treatment and/or at the last available data point for participants bilirubin levels were trending down or normalized.

8.13 AEs of Special Interest

Despite significant ALT and bilirubin elevations at baseline, there were no adverse events of special interest identified. No participant had suspected drug-induced liver injury. No participant had a post-nadir ALT elevation > 3 × ULN with total bilirubin > 2 × ULN during

the Treatment Period. No participant experienced hepatic decompensation or failure adverse events on treatment. No participant experienced hepatocellular carcinoma. No new liver safety signals were identified.

8.14 Subgroup Analysis

The incidence of adverse drug reactions was low and there were no unexpected clinically important differences in safety amongst the following subgroups:

- Baseline HCV RNA (< LLOQ or ≥ LLOQ)
- Age (< 65 or ≥ 65 years)
- Baseline HCV/HIV-1 co-infection status (HCV mono-infected or HCV/HIV-1 co-infected)
- History of non-prescribed illicit drug use
- History of non-prescribed illicit injection drug use
- PWID Classification
- History of opiate substitution therapy
- Categorization of baseline HCV infection status based on HCV-specific virology and serology laboratory results

8.15 Day 120 Safety Update Report

The Applicant submitted a Day 120 (4-Month) Safety Update Report on April 15, 2025, which made reference to the most recent complete Glecaprevir/Pibrentasvir (MAVYRET) 1-year PSUR and any new safety information about MAVYRET relevant to the acute HCV indication identified from July 26, 2024 through a data cutoff date of March 28, 2025 (i.e.,3 weeks prior to 120 days post sNDA submission). The Agency had agreed to this alternative approach to meeting the Day 120 Safety Update requirement during pre-NDA discussions because all visits for the M20-350 trial were complete at the time of sNDA submission and all M20-350 safety data were included with the sNDA.

The referenced PSUR covered the interval July 26, 2023 to July 25, 2024 and was submitted October 3, 2024. and reviewed on January 24, 2025 as no action indicated with no comments the PSUR contained no new safety data.

Per the Applicant, review of all postmarketing data covering the period July 26, 2024 through March 28, 2025 revealed no new safety signals or unexpected trends for either the chronic or acute HCV infection indications. However, (b) (4) [redacted] The Applicant stated that they will provide the assessment to FDA only if new safety information is identified.

The FDA will ask the Applicant to submit the comprehensive safety assessment to the NDA when available, regardless of whether new safety information is identified. Of note, current MVYRET labeling includes information from Study DORA-Part 2 in which one of the

pediatric participant discontinued treatment due to an adverse reaction of erythematous rash (Grade 3).

The FDA will continue routine pharmacovigilance monitoring for MAVYRET use.

9. Patient Reported Outcome Assessments

Although no patient-reported outcomes (PROs) were included as endpoints in Study M20-350, two instruments were used to assess patient perspectives at Baseline, Week 8, and Post-Treatment Week 12: EQ-5D-5L and Fatigue Severity Scale (FSS).

- The FSS, consisting of nine questions on a 7-point Likert scale, assesses fatigue impact on functioning, with higher scores indicating greater fatigue impact. The FSS also includes a separate Visual Analog Scale (VAS) wherein participants rate their perception of overall fatigue.
- The EQ-5D-5L evaluates health status preference across five dimensions, each rated on five severity levels. Responses are converted into a single health utility index score, with higher scores indicating better health. The EQ-5D-5L includes a separate VAS wherein participants rate their perception of overall health.

As the data generated from these PROs were not included as endpoints in the open-label single arm trial, the review team did not perform an independent analysis of the PRO data. Per the Applicant, there were no relevant mean changes in the EQ-5D-5L from baseline to final treatment or post-treatment visits. The Applicant reports small positive changes in the EQ-5D-5L VAS Score and FSS Total Score. Results of the FSS VAS were not included in the CSR.

The FDA reviewer concludes that results of the PRO data do not indicate any concerning quality of life data signals. The clinical significance of the small improvements in the EQ-5D-5L VAS and FSS Total Scores are uncertain, especially in the context of an open-label, single arm trial.

10. Advisory Committee Meeting

An Advisory Committee Meeting was not held for these supplemental NDA applications. No significant review issues were raised that would necessitate an advisory committee discussion.

11. Pediatrics

As this efficacy supplement seeks a new indication (treatment of acute HCV infection), the application triggers PREA.

The Applicant requested a partial waiver for pediatric patients ages birth to less than 3 years of age because necessary clinical studies in this age group are impossible or highly impracticable; the number of patients requiring treatment in this age group is very small due to a high rate of

spontaneous HCV clearance and lack of significant disease progression in children younger than 3 years of age.

Adolescents were eligible to participate in Study M20-350, the Phase 3b clinical trial designed to support the proposed indication for the treatment of acute HCV infection. Thus, the Agreed-upon-iPSP planned (b) (4) the Applicant revised their extrapolation plan to include the adolescent patient population. Efficacy data from adults with acute HCV infection, along with PK, safety, and efficacy data from adults and pediatric patients with chronic HCV infection were leveraged to extend the acute HCV indication to pediatric patients 3 years of age and older.

Please refer to **Section 5 Clinical Pharmacology** for more information about the Applicant's extrapolation approach. As described above, the dose and duration of treatment for acute and chronic HCV infection are identical. Additionally, the Division has determined that the HCV disease course and response to HCV treatment with DAAs (acute or chronic infection) is similar between children (3 and older) and adults. Further, the previously reviewed PK and safety data in adolescents from DORA Part 1 established the exposure and safety of GLE/PIB to be similar between adults and adolescents. DORA Part 2 established efficacy and safety in participants aged 3 years to less than 12 years for the MAVYRET oral pellet formulation.

The revised pediatric plan was discussed with the Pediatric Review Committee (PeRC) on May 6, 2025. The PeRC granted the partial waiver for pediatric patients ages birth to less than 3 years of age because necessary clinical studies in this age group are impossible or highly impracticable due to low incidence of infection in this age group. The PeRC also agreed that this product has been fully assessed (via extrapolation) in pediatric patients 3 to less than 18 years of age and the labelling will be updated accordingly.

12. Other Relevant Regulatory Issues

- All trials were conducted under Good Clinical Practice (GCP).
- No inspections were conducted for this supplement; inspections were conducted for the original NDA 209394.
- Financial disclosures were submitted and reviewed. One investigator held disclosable financial arrangements but did not enroll any participants. See the Clinical Investigator Financial Disclosure Table (**Appendix 1**) for further details.
- There are no outstanding regulatory issues.

13. Labeling

Revisions to the Applicant's proposed label have been discussed and agreed upon by the Applicant. Labeling negotiations and changes in the updated label are summarized herein.

Based on data included in this efficacy supplement related to the new indication for acute HCV infection, the Applicant proposed adding the new indication, dosing clarification,

safety and efficacy data in Sections 1, 2, 6, 8, 12 and 14. The Applicant also originally proposed [redacted] (b) (4) participants including those with HIV-1 coinfection, persons who inject drugs (PWID) and those on medication assisted treatment (MAT) for Opioid use disorder. As the safety and efficacy information for the sub-populations of those participants with acute HCV infection was similar to that of previously studied subpopulations with chronic HCV infection, a statement to this effect was added to each section. This improved the readability of the label and avoided presentation of the data in sometimes very small sub-populations, which can skew findings. Additionally, updates were made to some of the existing subsections to specify "chronic HCV infection" versus "HCV infection" more broadly where appropriate.

A summary of the major changes made to the prescribing information is listed below:

SECTION 1 - INDICATIONS AND USAGE

- Added indication for treatment of acute HCV infection in adults and pediatric patients 3 years and older.

SECTION 2 - DOSAGE AND ADMINISTRATION

- Added information for dosing for acute HCV infection. Modified Tables #1 and #2 to clarify that the variables driving the duration of treatment refer to the current infection.

SECTION 6 - ADVERSE REACTIONS

- Added subsection on adverse reactions in subjects with acute HCV infection.
- Additional baseline demographic and disease characteristic data were added within this subsection to better define the enrolled patient population.
- Under the subsection "Laboratory Abnormalities" added a paragraph describing bilirubin and ALT changes on treatment.

SECTION 8 - SPECIAL POPULATIONS

- Section 8.4 (Pediatric Use) was updated to include the rationale for extending labeling for the treatment of acute HCV infection indication to include pediatric patients ages 3 and older.

SECTION 12 – CLINICAL PHARMACOLOGY

- Added a statement in the section titled *Pediatric Patients* clarifying that no clinically meaningful differences in exposures are expected between acute and chronic HCV patients.
- In Section 12.4 Microbiology, the sponsor added a summary of the impact of baseline HCV amino acid polymorphisms on treatment outcomes in clinical trial M20-350. The summary, which was placed in the incorrect sub-section, was moved to the appropriate sub-section ("*Effect of Baseline HCV Amino Acid Polymorphisms…"*) and revised to include additional information on the NS3 and NS5A positions and denominators considered in the analyses.
- In Section 12.4 Microbiology, the sub-section "*Persistence of Resistance-Associated Substitutions"* was updated to remove this statement: [redacted] (b) (4)

(b) (4)

The summary statement on persistence of NS5A resistance-associated substitutions was updated to read as follows: *"Certain NS5A inhibitor resistance-associated substitutions have been found to persist for >1 year in some patients.*

SECTION 14 – CLINICAL STUDIES

- A new subsection 14.11 titled "Adults with Acute HCV Infection" was added describing the efficacy results from Study M20-350. This includes details on the study design, patient characteristics, and efficacy outcomes.

PATIENT INFORMATION

- The "What is MAVYRET?" section was updated to include treatment of acute HCV infection in addition to chronic HCV infection.

14. Postmarketing Recommendations

No Postmarketing Requirements and Commitments are indicated based on the data reviewed.

15. Recommended Comments to the Applicant

No additional comments need to be communicated to the Applicant at this time.

APPENDIX 1- Clinical Investigator Financial Disclosures

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 158		
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 ☒	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:	Yes ☒	No ☐ (Request explanation from applicant)

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