Official Protocol Title:	A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/ Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection
NCT number:	NCT03379506
Document Date:	16-Feb-2018

Title Page

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Protocol Title: A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection

Protocol Number: 079-02

Compound Number: MK-5172

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

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Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND NUMBER: [110,261]

EudraCT NUMBER: [2015-003006-16]

Approval Date: 16-Feb-2018

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 02

Overall Rationale for the Amendment:

This amendment incorporates a number of minor changes throughout to improve the clarity of the protocol and three major changes:

1. C_{trough} at Week 4 was added as a primary endpoint.
2. Dosing by weight bands for Mini Age Cohort 3 and Expanded Age Cohorts 1 and 2/3.
3. Revised DILI and ECI language.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Main Changes		
1 – Synopsis, Objectives/Hypotheses and Endpoints 4 – Objectives / Hypothesis and Endpoints 5.4.2.4 – Pharmacokinetic Endpoints 10 – Statistical Analysis Plan	Drug concentration immediately pre-dose (C_{trough}) at Week 4 was added as a primary endpoint	C_{trough}, a relevant pharmacokinetic (PK) endpoint, was raised to a primary endpoint to fully characterize the PK profile. Additional blood from participants will not need to be collected in order to analyze C_{trough}.

Section # and Name	Description of Change	Brief Rationale
5.1 – Overall Design 5.5.1 – Starting Dose for this Trial 5.5.1.3 – Dose in Mini Age Cohort 3 and Expanded Age Cohorts 1, 2, and 3 7.1 – Treatments Administered 10.6.2 – Modeling and Simulation for Dose Selection 10.10 – Subgroup Analyses	The text was updated to include the use of weight bands (which will be determined based on PK analyses) for dose recommendations in Mini Age Cohort 3 and the Expanded Age Cohorts. In Section 10.10, weight bands have been added as a category of subgroup analyses.	Added to improve the precision of pediatric dosing recommendations made by the study.
9.3.7 – Events of Clinical Interest (ECI)	The following revisions were made to liver-related ECIs: • In ECI #2, "from the initiation of study therapy" was replaced with "**after** initiation of study therapy" • In ECI #3, ">3X ULN from the initiation of study therapy" was replaced with "**>100 IU/L after** initiation of study therapy"	An ALT/AST threshold of >100 IU/L is a clinically meaningful threshold for evaluation of potential drug induced liver toxicity for pediatric participants. Using a numerical trigger for evaluation rather than fold ULN, ensures a uniform approach to evaluation of ALT and AST elevations. Use of the word "after" rather than "from initiation" ensures that the elevation being captured occurs after Day 1 of therapy.

Section # and Name	Description of Change	Brief Rationale
Other Changes		
2 – Schedule of Activities (SoA)	Removed heart rate and blood pressure as examples of vital signs that will be collected from the first column of the table.	These were removed to clarify that comprehensive vital sign data will be collected, not just heart rate and blood pressure. Vital signs being collected were added to the "Notes" column.
3.3 – Benefit/Risk Assessment	Details of study procedures to monitor for elevations in alanine aminotransferase (ALT) were added.	Revisions made to allow investigators to more easily identify the benefit/risks to the participant and the protocol-defined procedures in place for monitoring potential risks
5.1 – Overall Design	Enrollment requirements for the mini and expanded age cohorts were removed from the text and summarized in a table.	Presentation of enrollment requirements revised to improve readability of section.
5.1.1 – Study Diagram	The diagram was updated to be consistent with Table 2.	Consistent with the enrollment requirements for each Age Cohort in Table 2.
5.4.2.3.2 – Late ALT Elevations and Hepatic ECI Resulting in a Pause in Enrollment 8.1 – Discontinuation of Study Treatment	Bulleted criterion in each section was revised to remove "Grade 4 laboratory abnormality".	Grading of adverse events (AE), including laboratory AEs, are reported by the investigator as mild, moderate, or severe as described in Section 9.3 of the protocol and not as a numerical scoring system. Any Grade 4 event would be reported by this methodology.

Section # and Name	Description of Change	Brief Rationale
6.1 – Inclusion Criteria	Inclusion criterion #5 (a) (iii) was revised to add that absence of cirrhosis can be determined by local clinical standards during screening as assessed by the investigator.	This change was made to clarify that absence of cirrhosis can be determined by local clinical standards that includes physical examination during screening in combination with laboratory evaluation during screening and/or imaging test within 6 months of screening, as assessed by the investigator.
	Inclusion criterion #5 (b) (iii) was revised to add that cirrhosis can be determined by local clinical standards during screening as assessed by the investigator.	This change was made to clarify that the presence of cirrhosis can be determined by local clinical standards that includes physical examination during screening in combination with laboratory evaluation and/or imaging test as assessed by the investigator.
	The following note was removed from inclusion criterion #5: Computed tomography or magnetic resonance imaging obtained as part of clinical care may be used in place of ultrasound, if available.	This change was made to remove an errant note from inclusion criterion #5.
	The term “legally acceptable representative” in inclusion criterion #10 was revised to “legally acceptable representative(s)”.	This change was made to address potential site-specific requirements that both parents need to sign the informed consent before the child can participate in a clinical trial.

Section # and Name	Description of Change	Brief Rationale
6.2 – Exclusion Criteria	1. A note was added to criterion #2 to specify use of +1 for the bilirubin category of the Child-Pugh calculation for participants with Gilbert's syndrome. 2. Criterion #7c was updated to specify that participants with "uncontrolled" celiac sprue disease are excluded. 3. "Failure to thrive" was added to the list of excluded medical conditions in criterion #7e.	1. Added to improve clarity of the protocol; mild bilirubin elevations are found in patients with Gilbert's syndrome, which is common and not reflective of an underlying advanced liver disease. 2. Wording refined as patients with controlled disease do not have malabsorption. 3. This change was made to provide an additional medical exclusion of children with an unusually low weight that might impact PK.
6.3.1 – Meals and Dietary Restrictions 7.1 – Treatments Administered 9.1.8.1 – Timing of Dose Administration	The type of soft food dosing vehicle for the pediatric formulation was updated to applesauce, pudding, or yogurt.	This change was made to clarify the type of soft food acceptable for use in this study.

Section # and Name	Description of Change	Brief Rationale
7.1 – Treatments Administered	A statement was added to specify that, following assignment of formulation, participants may not change from FDC tablets to pediatric formulation or from pediatric formulation to FDC tablets.	Added to improve clarity of the protocol.
	The description of the pediatric formula single entity packet was updated to clarify that the Sponsor's product number (MK-8742 for EBR and MK-5172 for GZR) will be included on the label.	This change was made to clarify that MK-8742 represents EBR and MK-5172 represents GZR on the label.
7.7 – Concomitant Therapy	1. The table containing prohibited medications was updated to reflect that all statins are prohibited during the dosing period of the study. 2. Text that repeated a prohibited medication ("modafinil") was deleted from the table.	1. Statins are excluded in order to minimize the number of variables that impact the PK of EBR/GZR. 2. Redundant content removed.
	"Including but not limited to" was added to the list of prohibited strong CYP3A inhibitors by participants in the Mini Age Cohorts.	To improve clarity of the protocol.
8.1 – Discontinuation of Study Treatment	Repeated bullet has been deleted.	Redundant content removed.
9.1.12 – Calibration of Equipment	Removal of text referring to critical equipment.	Textual revisions were applied to clarify investigator responsibility for calibration and maintenance of trial equipment.

Section # and Name	Description of Change	Brief Rationale
9.6.1 – Blood Collection for Plasma EBR/GZR	1. Instructions were added for participants receiving pediatric formulation to record the following information in the Study Medication and Meal Diary (SMD) for all doses: a) the soft food that EBR/GZR granules were mixed into and b) the pediatric formulation food consumption timeframe (ie, the time from mixing of medication into the soft food vehicle to complete consumption of all granules that were mixed into the soft food). Sites should also enter this information into the eCRF.	1. Soft food vehicle information may be considered as part of the PK analyses in order to ascertain whether the type of food vehicle or the duration pediatric granules are dispersed within the food vehicle impact PK.
	2. The text was revised to clarify that meal data entry for the pre-dose PK sample on Day 1 is not required.	2. To improve clarity of the protocol.
	3. The timing for recording meal data on the day prior to the predose PK visit and on the day of the visit was updated.	3. The timeframe for collection of meal data around the dose was revised to represent the timeframe for which meals can impact PK results.
9.11.1 – Screening	An abnormal FibroScan result at Screening was deleted as an exclusionary criterion that could be retested	This change was made to correct an error. Abnormal FibroScan results at screening may not be repeated.

Section # and Name	Description of Change	Brief Rationale
9.11.2 – Treatment Period	1. The description of the packaging of open-label EBR/GZR FDC tablets was revised. "Blister card(s)" was replaced with "container(s)". 2. A reference to the soft food information to be recorded in the SMD for participants on EBR/GZR pediatric formulation was added.	1. The final packaging may be in the form of "blister cards" or "bottles" depending on geographic region. Therefore, the word "container" is inclusive for all packaging types. 2. Consistent with the soft food information instructions for the SMD added to Section 9.6.1.
9.11.4 – Discontinued Participants Continued to be Monitored in the Study	Participants who have met virologic failure criteria will also need to be identified as having a treatment-emergent resistance associated substitution in order to be eligible for follow-up in protocol MK-5172-017	Updated to clearly define participants who require additional follow-up to assess persistence of resistance following DAA therapy.
10.4.1.1 – Pharmacokinetic Endpoints	Included statement that the meal and soft food vehicle information may be considered in PK analyses.	This statement was added to improve clarity of the protocol regarding the purpose of meal and soft food information collection in this study.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized.

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LIST OF FIGURES

1. Synopsis

Protocol Title:

A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection

Short Title:

The Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Pediatric Participants with Chronic Hepatitis C Infection

Objectives/Hypotheses and Endpoints:

In pediatric participants (aged 3 to <18 years) with chronic hepatitis C genotype (GT) 1 or GT4 infection with or without compensated cirrhosis.

- GT1-infected participants who are treatment-naïve (TN) or treatment-experienced (TE).
- GT4-infected participants who are TN and have hepatitis C virus (HCV) ribonucleic acid (RNA) <800,000 IU/mL.

Objective/Hypothesis	**Endpoint**
There are no hypotheses to be tested in this trial.	
Primary	
• **Objective**: To evaluate the steady-state EBR and GZR pharmacokinetics (PK) in children and adolescents grouped by age.	• Week 4 $AUC_{0-24,}$ maximum observed drug concentration (C_{max}), drug concentration immediately pre-dose (C_{trough}), and apparent clearance (CL/F).
Secondary	
• **Objective**: To evaluate the safety and tolerability of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age.	• Number of participants experiencing adverse events (AEs). • Number of participants discontinuing study drug due to AEs.
• **Objective**: To evaluate the efficacy of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age, as assessed by the proportion of participants achieving sustained virologic response 12 weeks after the end of all study therapy (SVR_{12}).	• SVR_{12}: defined as HCV RNA <lower limit of quantification (LLOQ) (either target detected, but unquantifiable [TD(u)] or target not detected [TND]) 12 weeks after the end of all study therapy.

Overall Design:

Study Phase	Phase IIb
Clinical Indication	Treatment of HCV infection
Population	Pediatric participants aged 3 to less than 18 years of age with chronic Hepatitis C GT1 or GT4 infection.
Study Type	Interventional
Type of Design	Non-randomized, single arm, multiple cohort, uncontrolled
Type of Control	No active control
Study Blinding	Unblinded Open-label
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 112 weeks from the time the first participant signs the informed consent/assent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 56 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Pediatric participants with HCV GT1a without baseline NS5A resistance associated substitution (RAS) at position 28, 30, 31, and/or 93 or GT1b/1-other infected TN or pegylated-interferon/ribavirin (PR) TE cirrhotic or noncirrhotic (NC). Pediatric participants infected with GT4 (with HCV RNA <800,000 IU/mL) who are TN can also be enrolled. Participants will receive EBR/GZR for 12 weeks with 24 weeks of follow-up. The trial will enroll participants into three Age Cohorts: Age Cohort 1: aged 12 years to less than 18 years Age Cohort 2: aged 7 years to less than 12 years Age Cohort 3: aged 3 years to less than 7 years Age Cohort 1 will initially be administered Fixed Dose Combination (FDC) tablets (EBR 50 mg/GZR 100 mg). Age Cohort 2 and 3 will be administered pediatric formulation product (dosage to be informed by trial).

	Participants in Mini Age Cohort 1 will receive a single placebo to EBR/GZR FDC tablet prior to allocation in order to demonstrate the ability to swallow a tablet the size and shape of the FDC. This will also apply to participants in Expanded Age Cohort 1 if it is determined by PK analysis that Expanded Age Cohort 1 will also receive the adult FDC dose.
Duration of Participation	Each participant will participate in the trial for approximately 42.5 weeks from the time the participant signs the Informed Consent/Assent Form through the final contact. After a screening phase of up to 45 days (6.5 weeks), each participant will receive the assigned treatment for approximately 12 weeks followed by 24 weeks of standard follow-up.

A list of abbreviations used in this document can be found in Appendix 1. Study governance considerations are outlined in Appendix 3.

2. Schedule of Activities (SoA)

Trial Period	Screening	Treatment							Follow-up						Unscheduled		Notes
		Day 1	TW 2	TW 4	TW 6	TW 8	TW 10	TW 12	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Unsched/ HCV VF Conf Visit	Early Discon Visit	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Day 1 procedures to be performed prior to 1st morning dose unless otherwise specified. FW8, FW16, & FW20 are via phone contact w/the participant or the participant's legally acceptable representative to make sure he/she is doing well and FW24 visit reminder**
Scheduled Hour, Day, Week, etc., and Window:	**-45**	**NA**	**TW4: -3 to +3 days All other TW: -7 to +7 days**						**-2 to +2 weeks**						**NA**		**Participants should be allocated within a 45 day screening window**
Administrative Procedures																	
Informed Consent/assent	X																ICF: Each legally minor participant who assented at the beginning of the trial and become legally adult by the local/country law, during the trial period, will have to consent again. Study coordinator will check the participant's age periodically.
Informed Consent for Future Biomedical Research (FBR)	X																Participation in FBR is voluntary and is not required in order to participate in the study.
Biological Parental Consent to Use and Disclose Personal Data	X																The height of the biological parents will be collected between screening and Day 1. If biological parents are unable to be reached during that period the participant may continue in the trial. Later attempts during the trial will be made to collect these data. Biological parental consent must be signed prior to obtaining, using, and disclosing their personal data. The participant may continue in the study without these data and/or consent to obtain, use, and disclose parental personal data.
Inclusion/Exclusion Criteria	X																
Participant Identification Card	X																
Medical History	X																
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Only non-study HCV medications will be queried during Follow-up weeks
Treatment Allocation		X															
Distribute Study Medication and Meal Diary (SMD) and review instructions		X	X	X	X	X	X										
Review SMD			X	X	X	X	X	X								X	

Trial Period	Screening	Treatment							Follow-up						Unscheduled		Notes
		Day 1	TW 2	TW 4	TW 6	TW 8	TW 10	TW 12	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Unsched/ HCV VF Conf Visit	Early Discon Visit	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Day 1 procedures to be performed prior to 1st morning dose unless otherwise specified. FW8, FW16, & FW20 are via phone contact w/the participant or the participant's legally acceptable representative to make sure he/she is doing well and FW24 visit reminder**
Scheduled Hour, Day, Week, etc., and Window:	**-45**	**NA**	**TW4: -3 to +3 days All other TW: -7 to +7 days**						**-2 to +2 weeks**						**NA**		**Participants should be allocated within a 45 day screening window**
Reconcile Study Medication/Assess Compliance with EBR/GZR			X	X	X	X	X	X								X	
Drug Administration																	
Placebo to EBR/GZR (FDC) Administration	X																Placebo is given once prior to allocation to participants in Mini Age Cohort 1 to test whether the participant can swallow the tablet. If it is determined by PK analysis that Expanded Age Cohort 1 will also receive the adult FDC dose, then placebo will be given once prior to allocation to participants in Expanded Age Cohort 1. If the participant cannot swallow the placebo tablet then they cannot be allocated into the trial. Placebo tablets are different in color but identical in size and shape to the active EBR/GZR FDC tablets.
Dispense EBR/GZR (open label)		X	X	X	X	X	X										
HCV Evaluations																	
HCV Genotype Determination	X																
Liver imaging	X																For cirrhotic participants only, imaging (eg, ultrasound) is required within 6 months prior to allocation to rule out HCC.
HCV RNA Level	X			X		X		X	X		X			X	X	X	If a participant is confirmed HCV viral failure during therapy (ie, break through), then the sample collection for HCV RNA is not needed for the early discontinuation visit. Leftover main study plasma from HCV RNA will be stored for FBR if the participant/legally acceptable rep consents to FBR.

Trial Period	Screening	Treatment							Follow-up						Unscheduled		Notes
		Day 1	TW 2	TW 4	TW 6	TW 8	TW 10	TW 12	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Unsched/ HCV VF Conf Visit	Early Discon Visit	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Day 1 procedures to be performed prior to 1st morning dose unless otherwise specified. FW8, FW16, & FW20 are via phone contact w/the participant or the participant's legally acceptable representative to make sure he/she is doing well and FW24 visit reminder**
Scheduled Hour, Day, Week, etc., and Window:	**-45**	**NA**	**TW4: -3 to +3 days All other TW: -7 to +7 days**						**-2 to +2 weeks**						**NA**		**Participants should be allocated within a 45 day screening window**
Plasma for HCV Viral Resistance/Resistance Associated Substitutions (RAS)	X								X		X			X	X	X	Blood samples will be collected for HCV RAS testing at screening (to assess NS5A polymorphisms at amino acid positions 28, 30, 31, or 93); results for GT1a participants must be available prior to allocation. Viral resistance testing will be performed at screening to determine pre-existing RASs to EBR and GZR. Samples for resistance testing are also collected at follow-up visits and at the virologic failure confirmation visit (should this occur). If a participant is confirmed HCV viral failure during therapy (ie, break through), then the sample collection for HCV RAS is not needed for the early discontinuation visit. Leftover main study plasma from HCV Resistance may be used for FBR only if the participant/legally acceptable representative signed for FBR consent.
Safety Procedures																	
Comprehensive Physical Examination	X	X															A comprehensive PE will be done at screening and baseline (Day 1). For all other visits a focused PE will be conducted when clinically indicated.
Focused Physical Examination				X		X		X			X			X		X	A comprehensive PE will be done at screening and baseline (Day 1). For all other visits a focused PE will be conducted when clinically indicated.
Height	X	X						X			X			X			
Weight	X	X		X		X		X			X			X			
12-Lead ECG	X																
Vital Signs	X	X		X		X		X	X		X			X		X	Includes pulse, blood pressure, respiratory rate, and body temperature.

Trial Period	Screening	Treatment							Follow-up						Unscheduled		Notes
		Day 1	TW 2	TW 4	TW 6	TW 8	TW 10	TW 12	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Unsched/ HCV VF Conf Visit	Early Discon Visit	
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Day 1 procedures to be performed prior to 1st morning dose unless otherwise specified. FW8, FW16, & FW20 are via phone contact w/the participant or the participant's legally acceptable representative to make sure he/she is doing well and FW24 visit reminder**
Scheduled Hour, Day, Week, etc., and Window:	**-45**	**NA**	**TW4: -3 to +3 days All other TW: -7 to +7 days**						**-2 to +2 weeks**						**NA**		**Participants should be allocated within a 45 day screening window**
Height of Biological Parent		X															The height of the biological parents will be collected between screening and baseline. If biological parents are unable to be reached during that period the participant may continue in the trial. Later attempts will be made to collect these data. Biological parental consent must be signed prior to obtaining, using, and disclosing their personal data. The participant may continue in the study without these data and/or consent to obtain, use, and disclose parental personal data.
Date of menarche (females only)		X	X	X	X	X	X	X	X								Review at each visit as appropriate in prepubescent female participants. Once a date of menarche has been confirmed, the participant is considered to be a woman of childbearing potential (WOCBP) and the next 2 procedures (confirmation of birth control and urine pregnancy test) will apply.
Participant confirmation of birth control (WOCBP only)	X	X	X	X	X	X	X	X	X						X	X	
Urine Pregnancy Test (WOCBP only)	X	X		X		X		X	X						X	X	
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All AEs that occur after the consent/assent form is signed but before allocation must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of allocation through 14 days following cessation of treatment, all AEs must be reported by the investigator. The reporting timeframe for AEs meeting any serious criteria is described in Section 9.3.4. All protocol specified ECIs will be collected throughout the trial as listed in Section 9.3.7.
Coagulation	X	X				X		X			X			X	X	X	

Trial Period	Screening	Treatment							Follow-up						Unscheduled		Notes
		Day 1	TW 2	TW 4	TW 6	TW 8	TW 10	TW 12	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Unsched/ HCV VF Conf Visit	Early Discon Visit	
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Scheduled Hour, Day, Week, etc., and Window:	**-45**	**NA**	**TW4: -3 to +3 days All other TW: -7 to +7 days**						**-2 to +2 weeks**						**NA**		**Participants should be allocated within a 45 day screening window**
Chemistry (complete)	X	X		X		X		X			X			X	X	X	
Chemistry (abbreviated)			X		X		X		X								Abbreviated blood chemistry includes only ALT, AST, Alkaline phosphatase, T. Bili, Albumin, GGT, CPK
Hematology	X	X		X		X		X	X		X			X	X	X	
HIV Serology	X																
Urinalysis		X		X		X		X	X							X	
Hepatitis B Virus Evaluations																	
HBsAg	X																
Anti-HBc	X																
Patient-reported Outcome																	
Palatability and Acceptance Assessment				X		X											

Trial Period	Screening	Treatment							Follow-up						Unscheduled		Notes
		Day 1	TW 2	TW 4	TW 6	TW 8	TW 10	TW 12	FW 4	FW 8	FW 12	FW 16	FW 20	FW 24	Unsched/ HCV VF Conf Visit	Early Discon Visit	
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Pharmacokinetics (PK)																	
EBR/GZR PK		X		X		X									X	X	Refer to Section 9.6.1 for details of PK sample collection timepoints for individual Age Cohorts. At Day 1 (Mini Age Cohort 1 only) and TW4 (all participants), an overnight stay is recommended to obtain PK samples over a 24-hour period (intensive PK). On all PK visits where a predose sample will be collected, the visit should occur prior to the participant's regular time for taking their study medication and the participant should withhold their dose until after the visit. For predose PK visits (ie, Day 1, Week 4, Week 8), if it is not feasible to schedule the visit prior to the participant's regular time for taking their study medication, the participant should withhold their dose until reporting to the clinic. The predose PK sample will be obtained and the dose will be administered at the clinic. If HCV viral failure confirmation visit is after the end of therapy, do not collect the PK sample at this visit.
Meal Information for PK		X		X		X											

3. Introduction

MK-5172 is a fixed dose combination (FDC) of elbasvir (EBR: an NS5A inhibitor) and grazoprevir (GZR: an NS3/4A protease inhibitor) which has been approved for the treatment of chronic hepatitis C virus (HCV) infection in adults.

3.1 Study Rationale

The purpose of this protocol is to assess pharmacokinetics (PK), safety, and efficacy of EBR and GZR in a population of pediatric HCV-infected participants aged 3 years up to 18 years. These data will be used to support dosing recommendations in the pediatric population. EBR/GZR with and without ribavirin (RBV) has been developed and approved for adults with chronic hepatitis C genotype (GT) 1 or 4. Diverse adult populations have been studied including those with cirrhosis, human immunodeficiency virus type 1 (HIV-1) co-infection, end stage renal disease, and prior treatment failure. Efficacy rates exceed 90% regardless of these underlying co-morbidities or patient characteristics.

Historically, children treated for HCV have had similar response rates as adults when given a similar regimen at the appropriate dose. The adult EBR/GZR PK model is highly predictive of clinical response (safety and efficacy in adults). Therefore pediatric patients are anticipated to have a similar safety and efficacy profile when given doses that achieve a similar exposure as that seen in adult patients. The intensive PK obtained at Treatment Week (TW) 4 will be used to update the adult population PK model to support dosing recommendations in the pediatric population.

3.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information including preclinical and clinical trial data for EBR/GZR.

3.2.1 Pharmaceutical and Therapeutic Background

MK-5172 is comprised of the following 2 direct-acting antiviral (DAA) HCV agents:

- EBR (elbasvir, MK-8742) is an HCV NS5A inhibitor.
- GZR (grazoprevir, MK-5172) is an HCV NS3/4A protease inhibitor.

Each MK-5172 FDC tablet contains EBR (50 mg) and GZR (100 mg) and is administered once daily (QD). Participants in Mini Age Cohort 1 (oldest Age Cohort) will receive the FDC tablet. This will also apply to participants in Expanded Age Cohort 1 if it is determined by PK analysis that Expanded Age Cohort 1 will also receive the adult FDC dose. The two younger age cohorts will receive EBR pediatric formulation and GZR pediatric formulation. See Section 7.1 for a description and dosing instructions of the EBR/GZR pediatric formulation.

3.2.1.1 Overview

Children with chronic hepatitis C are vulnerable to the same long-term health consequences as adults, including progressive liver damage, cirrhosis, and hepatocellular carcinoma (HCC). Developing an age appropriate, all-oral, well tolerated, short duration treatment regimen for HCV infected children is highly desirable for a population that is currently restricted to the current pediatric standard of care, pegylated-interferon with RBV (PR). In contrast to the current safe and convenient therapies available to adults, PR most commonly requires 48 weeks of therapy, with weekly injections. The therapy has many adverse events (AEs), including flu-like symptoms, anemia, and impairment of growth, while achieving a sustained virologic response (SVR) of only ~50%.

Epidemiology of Chronic Hepatitis C

Worldwide it is estimated that 3 to 4 million people are newly infected with HCV annually and 170 million are chronically infected [Hanafiah, K. M., et al 2013]. For those who are chronically infected, there is a lifetime risk of developing progressive liver damage, cirrhosis, and liver cancer. In the United States (US), approximately 2.2 to 3.2 million persons are estimated to have chronic HCV infection based on a national survey of the civilian, non-institutionalized population [Denniston, M. M., et al 2014].

Of the patients infected with HCV, many are children. Seroprevalence data for children aged 1 to 15 years in the US and in Western Europe are 0.6% and 0.8-1.3%, respectively. The prevalence is similar to the 20-30 year old population in each of these regions [Hanafiah, K. M., et al 2013]. Most studies that have investigated the seroprevalence of HCV in childhood fail to investigate whether HCV antibody-positive children are also HCV viremic. Extrapolating from adult studies, it is estimated that approximately 50-80% of those with positive HCV antibody are chronically infected and viremic [Aach, R. D., et al 2000] [Vogt, M., et al 1999].

Modes of Transmission of HCV in Pediatrics: Vertical transmission of HCV infection is the most common route of acquiring HCV infection in infants and children. In the US, there are approximately 7500 new cases per year from vertical transmission [Mack, C. L., et al 2012]. Mother to child transmission among HCV mono-infected women is approximately 5%. Although the risk is low for an individual, HCV infection is common, and thus accounting for a significant number of new infections in newborns annually. Among HIV-1/HCV co-infected women, vertical transmission can be as high as 25%. Other modes of transmission in pediatrics, include household contacts and most importantly, especially among adolescents, acquisition due to high risk behaviors such as injection drug use, tattoos, and piercings. For children younger than the age of 3 years, results from a prospective study following a birth cohort have shown that 17% had spontaneous viral clearance by age 2 and 24% had clearance by age 3 [England, K., et al 2005] [Narkewicz, M. R., et al 2007]. It is because of this early predilection for spontaneous clearance that treatment trials for children with chronic HCV do not include the age group from birth to age 3 years.

Therapy for Chronic Hepatitis C

The therapeutic goal of treatment of hepatitis C is the eradication of the virus with a halt in the progression of liver damage. Similarities in the treatment response characteristics of

chronic HCV in adult and pediatric populations support the premise that therapeutic advances demonstrated in adults will likely be applicable to children. Historically, children have benefited from a similar approach to treatment of chronic HCV as adults [Kelly, D. A., et al 2011] [Wirth, S., et al 2010]. As of 2017, high efficacy was observed in a Phase II trial and supported approval in children aged 12 to 18 of an all-oral DAA regimen of sofosbuvir/ledipasvir [Balistreri, W. F., et al 2016]. The observed efficacy in the pediatric population in this study was similar to that seen among adults treated with the same regimen. Children should benefit from the new generation of HCV treatments that are all oral, safe, and effective. These advances are substantial improvements compared to the current standard of care for children, which is 24 to 48 weeks of PR.

It is anticipated that EBR/GZR dosed to provide the same PK exposures achieved in the adult population will be an effective and safe pediatric HCV therapy for GT1 and GT4 infection, as indicated in adults.

3.2.2 Summary of Clinical Experience with EBR/GZR

3.2.2.1 Summary of Clinical Experience with EBR/GZR in Adults

EBR/GZR (50 mg/100 mg) ± RBV has demonstrated a favorable safety and efficacy profile in a diverse adult (≥18 years of age) population that included patients with compensated cirrhosis, chronic kidney disease, and HIV-1/HCV co-infection [Ferrante, S., et al 2015] [Lawitz, E., et al 2014] [Sulkowski, M., et al 2014] [Zeuzem, S., et al 2015] [Rockstroh, J. K., et al 2015] [Forns, X., et al 2015] [Buti, M., et al 2016] [Roth, D., et al 2015].

The data below provides an overview of the primary efficacy endpoint, sustained virologic response 12 weeks after the end of all study therapy (SVR_{12}), supporting final adult dosing and administration guidance.

- High response rates in GT1 and GT4 treatment-naïve (TN) subjects (SVR_{12} of 94-96%) treated with a 12-week, RBV free regimen.
- High response rates in GT1, and GT4 PR-treatment-experienced (TE) relapsers (SVR_{12} of 100%) treated with a 12-week, RBV free regimen.
- High response rates in GT1b PR-TE subjects who failed prior PR therapy due to either null or partial response (SVR_{12} 100%) when treated with a 12-week, RBV free regimen.
- High response rates in all GT1 and GT4 subjects treated for 16 weeks with a regimen of EBR/GZR with RBV.
- Response rates that are comparable in Childs-Pugh A cirrhotics and noncirrhotics.

In addition to the data above, a secondary analysis has been performed that demonstrates that incorporation of resistance testing for GT1a-infected participants can be used to optimize efficacy outcomes in the minority of GT1a-infected patients with baseline NS5A resistance-associated substitutions (RASs) who may have suboptimal efficacy with a 12-week EBR/GZR regimen. These data are shown below in Table 1 shows the integrated data and observed efficacy from the adult Phase II/III EBR/GZR development program when RAS

testing is incorporated into dosing and administration guidance for the GT1a population. The populations included in these integrated data include TN and TE patients with compensated cirrhosis, advanced chronic kidney disease, and both mono HCV infected and HIV-1/HCV co-infected patients.

Table 1 SVR12 of EBR/GZR (50 mg/100 mg) – MK-5172 Protocols 035, 048, 052, 060, 061, and 068

Regimen	Study Population	SVR_{12} OVERALL N	n	%
12 wks no RBV	1a TN or PR-TE Without BL RASs 28, 30, 31, 93†	450	441	98.0%
	1b TN or PR-TE	301	297	98.7%
	4 TN	55	54	98.2%
16 wks + RBV	1a TN or PR-TE With BL RASs 28, 30, 31, 93†	6	6	100%
	4 PR-TE	8	8	100%

Based on the modified Full Analysis Set population that excludes subjects who discontinued from the study for non-treatment-related reasons.

† In GT1a subjects, subjects without baseline NS5A sequencing information are excluded.

N: Number of subjects in population.

n: Number of subjects who achieved SVR_{12}.

BL = baseline; GT = genotype; PR = pegylated-interferon with RBV; RAS = resistance-associated substitution; RBV = ribavirin; SVR_{12} = sustained virologic response 12 weeks after the end of all study therapy; TE = treatment-experienced; TN = treatment-naïve.

Recommendations for dosing and administration of EBR/GZR have incorporated viral load, GT, treatment history, and GT/subtype and presence of baseline NS5A RASs. The recommendations adopted vary by region (eg, US vs European Union [EU]), in part due to the regional variability in availability of commercial RAS testing. In the US, the addition of RBV and lengthening the treatment duration to 16 weeks are recommended for the small subset of GT1a-infected patients with baseline RASs. In the EU, the addition of RBV and lengthening the treatment duration to 16 weeks are recommended for GT1a-infected patients with high viral load at baseline.

In this trial, in order to provide a simple regimen of 12 weeks without RBV (and applicable to both the EU and US prescribing information), only participants with HCV GT1 or with GT4 and HCV ribonucleic acid (RNA) <800,000 IU/mL will be enrolled. In addition, for those with GT1a infection, RAS testing will be used and only those without a baseline NS5A RAS at position 28, 30, 31, and/or 93 will be enrolled.

3.2.3 PK Background and Strategy

In the Phase II/III EBR/GZR development program, population PK, PK/pharmacodynamics (PD), and physiologically based pharmacokinetic (PBPK) modeling supported the proper dosing for a safe and efficacious adult regimen. The PK/PD modeling for safety and efficacy were used to define the clinical comparability bounds, based on an area under the time-concentration curve (AUC) of [0.4, 5.0] for GZR and [0.5, 2.0] for EBR. Application of these models and clinical bounds will be applied to this pediatric trial to support dosing of children aged 3 years up to 18 years.

3.2.3.1 EBR/GZR Metabolism

EBR elimination in humans is via a combination of excretion of parent compound as well as oxidative metabolism (mediated via cytochrome P4503A [CYP3A]) into feces, with minimal elimination into urine. EBR is a substrate of CYP3A and P-glycoprotein (P-gp) (minor contribution). EBR exhibits linear and dose-proportional PK across the 10-100 mg dose range. HCV patients and healthy participants receiving 50-100 mg QD have comparable plasma exposures at steady-state. Following administration of EBR 50 mg QD to HCV patients, the geometric mean (GM) apparent terminal half-life is ~24 hours and steady-state is achieved within 5 days. EBR exhibits moderate bioavailability (32%), with a time to maximum concentration (T_{max}) of ~3 hours.

GZR is eliminated via biliary excretion in the form of oxidative metabolism (mediated via CYP3A4) and as GZR (likely via biliary efflux transport) in humans. GZR is a substrate of CYP3A4, P-gp (minor contribution), and the liver uptake transporters organic anion-transporting polypeptide (OATP) 1B1/3. GZR has non-linear and greater than dose-proportional plasma PK in humans, likely attributed to saturation of CYP3A metabolism and OATP1B uptake at higher doses/exposures. Steady-state GZR plasma PK is ~2-fold greater in HCV patients than in healthy participants. Following administration of GZR 100 mg QD to HCV patients, the GM apparent terminal half-life is ~31 hours. In HCV patients, the HCV viral load decline associated with the first few weeks of administration of EBR/GZR results in decreased GZR exposure (likely due to improved liver function); therefore, steady-state in patients is achieved by about TW4. GZR exhibits moderate bioavailability (10-40%), with a T_{max} of ~2 hours.

3.2.3.2 Modeling and Simulation in Adults

Population PK, PK/PD, and PBPK models have been developed for EBR and GZR in support of the adult filings.

GZR is associated with exposure-dependent alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations that typically occur around TW 8-10. The efficacy endpoint for EBR and GZR of SVR_{12} is also exposure-dependent. Logistic regression PK/PD models for safety and efficacy have been established using adult data. During PK/PD model development, AUC was found to be the most predictive PK parameter for both safety and efficacy. Using the PK/PD models, the therapeutic bounds, based on AUC, were defined for EBR [0.5, 2.0] and GZR [0.4, 5.0].

Based on the EBR and GZR population PK models (N=3214 total patients and healthy participants), the impact of various intrinsic factors on the plasma PK of EBR and GZR were determined and are demonstrated in the forest plot in Figure 1. Several intrinsic factors affected EBR and/or GZR PK, but most changes were within the clinical comparability bounds, and therefore not clinically relevant. For example, low body weight (~37-66 kg) had an ~20% increase in AUC for both EBR and GZR, but the increase was well within the therapeutic window for both compounds. EBR/GZR are contraindicated in patients with Child-Pugh B and C cirrhosis.

PBPK models for EBR and GZR were previously developed, which incorporated the key absorption, distribution, metabolism, and excretion (ADME) and PK properties for both compounds (eg, OATP1B saturation for GZR) [M&S Analysis Rpt 2015][M&S Analysis Rpt 2015]. This modeling provided supportive mechanistic evidence and interpretation for the effect of intrinsic factors (eg, HCV infection, cirrhosis, Asian ethnicity) on the PK of EBR and GZR.

These data and models supported the approval of EBR/GZR in adults infected with HCV GT1 and/or 4 and will be updated and used to select appropriate doses for the pediatric population.

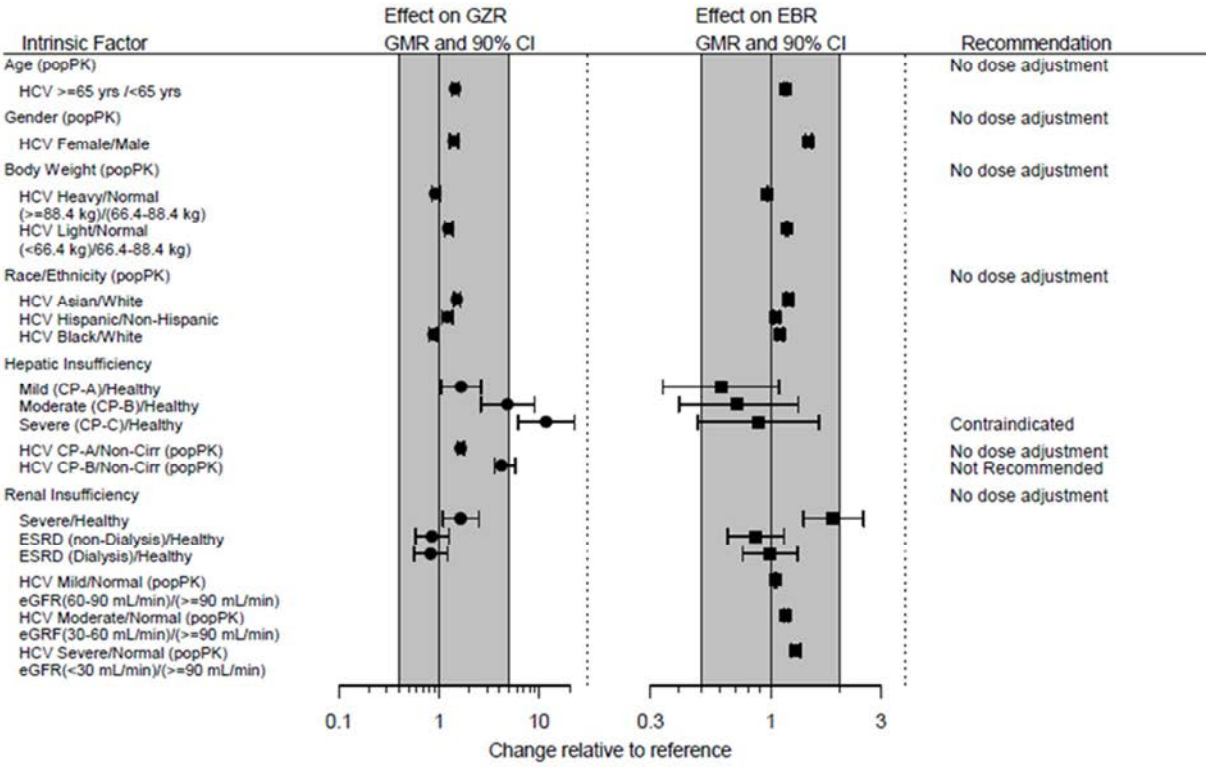

Figure 1 Impact of Intrinsic Factors on the AUC of EBR and GZR

The shaded area of Figure 1 represents the region of no clinically relevant effect.

3.2.4 Preclinical Trials Supporting a Pediatric Clinical Study

Prior to initiation of the pediatric clinical trial, pre- and postnatal developmental EBR and GZR monotherapy studies have been conducted and have not identified findings of concern in rats, rabbits, and dogs. In rats, dosing did not result in any effects on development, growth, behavior, reproductive performance, or fertility following oral administration to female rats from Gestation Day 6 through Lactation Day 20. In these studies, the highest maternal GZR exposure, area under the time-concentration curve over 24 hours (AUC_{0-24}) = 155 μM•hr represents approximately 31-fold the GZR clinical target AUC_{0-24} of 5 μM•hr in humans, and the highest maternal EBR exposure, AUC_{0-24} = 21.8 μM•hr (measured in pregnant females in the embryofetal developmental and toxicokinetic [TK] study in rats) represents approximately 16-fold the EBR clinical target AUC_{0-24} of 1.35 μM•hr in humans. Additionally, EBR and GZR placental and lactational transfer studies in rats and EBR and GZR placental transfer studies in rabbits showed distribution of EBR or GZR into rat and rabbit fetal plasma and rat milk. TK parameters obtained at different animal ages in the repeat-dose EBR and GZR monotherapy studies in rats and dogs did not indicate age-related differences in plasma systemic exposures. In rats, the first TK evaluation was performed in 7-week old animals (which corresponds to an approximate human age of 12 years), and the last TK evaluation was performed in 18-week old animals (adult animals). In dogs, the first TK evaluation was performed in 26- (EBR) or 32-week old (GZR) animals (which corresponds to an approximate human age of 15-17 years), and the last TK evaluation was performed in 56- (EBR) or 78-week old (GZR) animals (adult animals).

In conclusion, pre-clinical animal studies support the use of EBR and GZR in children.

3.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Elbasvir/Grazoprevir

In Phase I-III studies, 1,234 healthy volunteers, 66 non-HCV-infected persons with liver or kidney impairment, and 2,704 HCV-infected participants have been treated with any dose or regimen of EBR and/or GZR, with or without RBV. At a dose of EBR (50 mg) and GZR (100 mg), high efficacy and a favorable safety profile have been demonstrated in approximately 2,000 participants, including participants with cirrhosis, HIV-1/HCV-coinfection, chronic kidney disease, and history of prior HCV treatment failure.

ALT elevation is a safety signal associated with increased GZR exposures. Because of this, a plan has been developed to monitor for the signal. This protocol includes predefined monitoring of Events of Clinical Interest (ECI) (Section 9.3.7), specification of ALT levels that would require discontinuation of study treatment (Section 8.1), and predefined criteria for late ALT elevations and hepatic ECI which will result in a pause in enrollment (Section 5.4.2.3.2).

Additional details regarding specific benefits and risks for participants participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

4. Objectives/Hypotheses and Endpoints

In pediatric participants (aged 3 to <18 years) with chronic hepatitis C GT1 or GT4 infection with or without compensated cirrhosis.

- GT1-infected participants who are TN or TE.
- GT4-infected participants who are TN and have HCV RNA <800,000 IU/mL.

Objective/Hypothesis	Endpoint
There are no hypotheses to be tested in this trial.	
Primary	
• **Objective**: To evaluate the steady-state EBR and GZR PK in children and adolescents grouped by age.	• Week 4 AUC_{0-24}, maximum observed drug concentration (C_{max}), drug concentration immediately pre-dose (C_{trough}), and apparent clearance (CL/F).
Secondary	
• **Objective**: To evaluate the safety and tolerability of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age.	• Number of participants experiencing AEs. • Number of participants discontinuing study drug due to AEs.
• **Objective**: To evaluate the efficacy of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age, as assessed by the proportion of participants achieving SVR_{12}.	• SVR_{12}: defined as HCV RNA <lower limit of quantification (LLOQ) (either target detected, but unquantifiable [TD(u)] or target not detected [TND]) 12 weeks after the end of all study therapy.
Exploratory	
• **Objective**: To evaluate the efficacy of 12 weeks of treatment with EBR/GZR in children and adolescents grouped by age, as assessed by the proportion of participants achieving sustained virologic response 24 weeks after the end of all study therapy (SVR_{24}).	• SVR_{24}: defined as HCV RNA <LLOQ (either TD[u] or TND) 24 weeks after the end of all study therapy.

Objective/Hypothesis	Endpoint
• **Objective**: To evaluate the emergence of NS3 and NS5A RASs in participants with virologic failure.	• Treatment-emergent RASs to EBR/GZR.
• **Objective**: To evaluate the palatability and acceptability of treatment with EBR/GZR.	• Score on a palatability scale.
• **Objective**: To evaluate growth in children treated with EBR/GZR.	• Changes from baseline for height and weight by age.

5. Study Design

5.1 Overall Design

This is a non-randomized, single arm, multiple cohort, multi-site, open-label Phase IIb trial of EBR/GZR in pediatric participants aged 3 to less than 18 years with chronic HCV infection GT1b/1-other; GT1a without baseline NS5A RAS at positions 28, 30, 31, and/or 93; or GT4, to be conducted in conformance with Good Clinical Practice.

The goals of this Phase IIb trial are: 1) to define doses for EBR/GZR in children by assessing plasma PK concentrations that target a similar PK to that seen in adults receiving EBR 50 mg and GZR 100 mg. The PK target has been defined by the clinical PK comparability bounds, within which there were no clinically important differences for safety and efficacy; 2) to establish the tolerability, safety, and efficacy of the combination therapy in the pediatric HCV-infected population. All participants will receive EBR/GZR without RBV for 12 weeks.

The trial will enroll participants into three Age Cohorts:

1. Age Cohort 1 (aged 12 years to less than 18 years)
2. Age Cohort 2 (aged 7 years to less than 12 years)
3. Age Cohort 3 (aged 3 years to less than 7 years)

Each Age Cohort starts with a Mini Age Cohort of 7 participants before enrolling additional participants into the Expanded Age Cohort. The enrollment requirements for the Mini and Expanded Age Cohorts are shown in Table 2.

Table 2 Enrollment Requirements for Each Age Cohort

Age Cohort	Age Range	Enrollment Requirements	
		Mini Cohort	**Expanded Cohort**
1	12 to <18 years	• N=7 (to ensure at least 6 participants with evaluable PK) • At least 2 participants aged <14 years	• N=~15 • At least 3 participants aged 12 to <14 years • At least 3 participants aged 16 to <18 years
2	7 to <12 years	• N=7 (to ensure at least 6 participants with evaluable PK) • At least 2 participants aged <9 years	• N=~20 • At least 5 participants aged 7 to <12 years • At least 5 participants aged 3 to <7 years o At least 2 participants aged <5 years
3	3 to <7 years	• N=7 (to ensure at least 6 participants with evaluable PK) • At least 2 participants aged <5 years	

The enrollment of participants will occur as follows:

1. Mini cohorts of the two oldest Age Cohorts will enroll in the first wave of participants.
    a. Mini Age Cohort 1
    b. Mini Age Cohort 2

Enrollment into Mini Age Cohort 2 will follow Mini Age Cohort 1 by 2 to 3 weeks to allow time to review Day 1 PK (AUC) in a minimum of 6 participants of Mini Age Cohort 1 before enrolling Mini Age Cohort 2. The Week 4 intensive PK from the first two Mini Age Cohorts (N=~14), in addition to the Day 1 and Week 8 sparse PK, will be used to update the population PK and PBPK models to select optimal doses for Mini Age Cohort 3 and Expanded Age Cohort 1.

2. Mini Age Cohort 3 and Expanded Age Cohort 1 will enroll in the second wave of participants after optimal doses have been selected based on PK modeling results from the first wave of participants.
    a. Expanded Age Cohort 1 will enroll following completion of the PK modeling analyses; dosing will use the proposed dose for each component, EBR and GZR, and dose recommendation by weight bands will be used.
    b. Mini Age Cohort 3: PK modeling and simulation will be used to propose dosing for each component, EBR and GZR. Dose recommendation by weight bands will be used for Mini Age Cohort 3.

Data from the three Mini Age Cohorts and from Expanded Age Cohort 1 will be used to update the population PK and PBPK models in order to propose doses for Expanded Age Cohorts 2 and 3.

3. Expanded Age Cohorts 2 and 3 (Expanded Age Cohort 2/3)

    a. Expanded Age Cohorts 2 and 3 are combined as a single group Age Cohort 2/3. This age cohort will enroll following completion of the updated PK modeling analyses that incorporates PK data from all previous cohorts, including all 21 participants from the three Mini Age Cohorts and all 15 participants from Expanded Age Cohort 1. Dosing of Expanded Age Cohort 2/3 will use the modeling and simulation proposed dose for each component, EBR and GZR.

While age cohorts are used for the purposes of enrollment, dose recommendations by weight bands will be used for Mini Age Cohort 3 and the Expanded Age Cohorts. Weight bands will be determined based on the PK analyses.

Following the conclusion of this study and the Clinical Study Report (CSR) for the study, a final PK model will be developed that includes all PK data from participants aged 3 years up to 18 years, in addition to relevant adult data previously collected in the program. The final model and proposed pediatric dosing regimen will be summarized in a separate report.

PK samples will be collected in all pediatric participants according to the sampling scheme in Table 9. At Day 1 (Mini Age Cohort 1 only) and TW4 (all participants), an overnight stay is recommended to obtain PK samples over a 24-hour period (intensive PK).

In order to reduce PK variability, enrollment in the Mini Age Cohorts will be limited to noncirrhotic participants of non-Asian Race who are not currently taking methadone or strong CYP3A inhibitors. The Mini Age Cohorts will also exclude participants below a weight as described in the inclusion/exclusion criteria; the Expanded Age Cohorts will enroll a broader population as described in the inclusion/exclusion criteria.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

This trial will use an independent, external Data Monitoring Committee (eDMC) to monitor safety. Periodic safety analyses will be conducted and reviewed by the eDMC at regular intervals as outlined in the eDMC Charter.

The eDMC will make recommendations to the Sponsor to continue, modify, or end the trial according to Section 10 - Statistical Analysis Plan (SAP).

5.1.1 Study Diagram

The trial design is depicted in Figure 2.

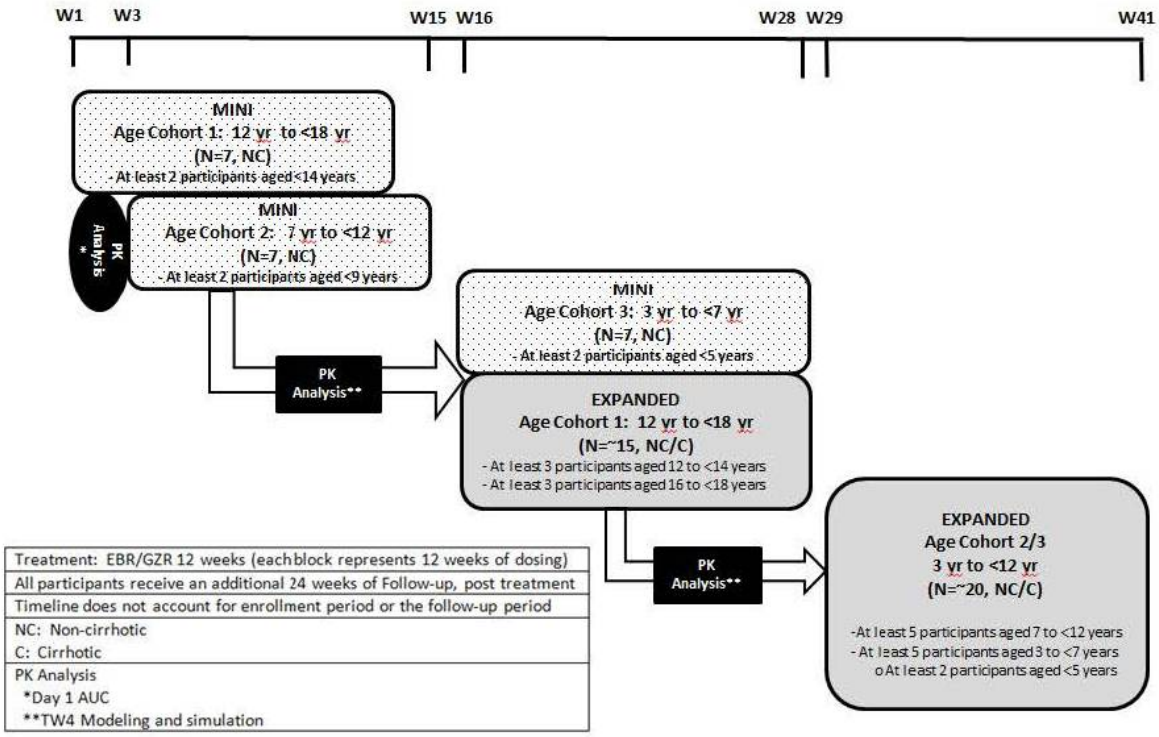

Figure 2 Trial Design

5.2 Number of Participants

Approximately 56 participants will be allocated as described in Section 10.1.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant (or the participant's legally acceptable representative) signs the informed consent/assent form (ICF). The overall study ends when the last participant completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up (i.e. the participant is unable to be contacted by the investigator).

5.3.1 Clinical Criteria for Early Study Termination

1. The eDMC recommends termination of the trial and the Executive Oversight Committee (EOC) agrees per Appendix 3 – Committee Structure - Data Monitoring Committee, Appendix 3 – Study and Site Closure, or as stated in the DMC charter.
2. The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Study Population

Participants in this trial will include noncirrhotic or compensated cirrhotic pediatric participants who are either TN or PR-TE and infected with HCV GT1b/1-other; or with HCV GT1a without a baseline NS5A RAS at position 28, 30, 31, and/or 93; or TN and infected with GT4 and HCV RNA <800,000 IU/mL; and who meet other inclusion/exclusion criteria as described in Section 6. Because PK exposure is independent of GT, the information obtained and doses proposed in this trial can be extrapolated to other GTs for final dosing and administration guidance. The final administration recommendations with regards to duration and need for RBV will be similar to the adult recommendations. Children enrolled in this trial will all be eligible for a 12-week RBV-free regimen, ie, this trial will enroll participants who are HCV GT1b/1-other; HCV GT1a without a baseline NS5A RAS at position 28, 30, 31, and/or 93; or are HCV GT4 with HCV RNA <800,000 IU/mL.

5.4.2 Rationale for Endpoints

5.4.2.1 Efficacy Endpoints

The measurement for efficacy in this trial is the plasma HCV RNA level. Long-term suppression of HCV RNA, typically reported as SVR, has been associated with improved outcomes in subjects with chronic hepatitis C infection as measured by biochemical and histological remission of liver disease. Most available data suggest that SVR following antiviral therapy reduces the risk of progression to cirrhosis and may prevent the development of severe liver complications and improve survival [Alberti, A. 2011].

The evaluation of efficacy in this trial is based on SVR_{12}, the same endpoint used for all investigational and approved DAAs. Since a high degree of concordance has been observed between SVR_{12} and SVR_{24} [Martinot-Peignoux, M., et al 2010], SVR_{12} is used as the primary endpoint for registration of DAAs. For this trial, an evaluation of efficacy based on SVR_{24} will be an exploratory analysis [Chen, J., et al 2013].

5.4.2.1.1 Measurement of HCV RNA

HCV RNA plasma levels will be measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from each participant at various time points prior to, during, and after dosing, as indicated in the SoA (Section 2).

They are also used to identify participants who meet HCV virologic failure criteria. HCV RNA levels are described as detailed in Table 3.

Table 3 Nomenclature for Describing HCV RNA Levels

Abbreviation	Definition	HCV RNA Level
TND	Target not detected	HCV RNA not detected
TD(u)	Target detected but unquantifiable	HCV RNA <LLOQ
TD(q)	Target detected, quantifiable	HCV RNA ≥LLOQ

Definition of Efficacy Endpoints

Efficacy will be defined at different timepoints during the trial. Specific endpoints are:

- **SVR_{12}** : Participant has HCV RNA <LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy.
- **SVR_{24}** : Participant has HCV RNA <LLOQ (either TD[u] or TND) 24 weeks after the end of all study therapy.

Definition of Virologic Failure

Lack of efficacy at different timepoints in the trial will be categorized as:

- **Non-response**: Participant has HCV RNA detected at end of treatment without HCV RNA <LLOQ having been achieved while on treatment (note that breakthrough is captured below).
- **Rebound**: Participant has a rebound defined as >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment and confirmed from a separate blood draw within 2 weeks.
- **Virologic breakthrough**: Participant has a confirmed HCV RNA ≥LLOQ (TD[q]) after being <LLOQ previously while on treatment. Confirmation is defined as an HCV RNA ≥LLOQ from a separate blood draw repeated within 2 weeks.
- **Relapse**: Participant has a confirmed HCV RNA ≥LLOQ (TD[q]) following end of all study therapy, after becoming undetectable (TND) at end of treatment. Confirmation is defined as an HCV RNA ≥LLOQ from a separate blood draw repeated within 2 weeks.

5.4.2.1.2 Viral Resistance Measurements

In this trial, RASs are defined as specific genetic substitutions that generate viral proteins that maintain function, but have reduced susceptibility to a DAA. As the presence of certain HCV RASs can lead to treatment failure, they are one of the most important considerations when treating with a DAA. Those genetic substitutions that impact efficacy outcomes may be present at baseline (ie, prior to therapy), or they may be treatment-emergent (ie, not detected at baseline, but which emerge and are selected over the course of therapy).

Blood samples for viral resistance assays are collected at:

- **Screening**: Testing will be done to assess for the presence of NS5A and NS3 RASs that have been associated with reduced efficacy for NS5A compounds (eg, ledipasvir, daclatasvir, EBR) or protease inhibitors (eg, simeprevir, boceprevir, telaprevir, GZR). In GT1a-infected participants, presence of NS5A RAS at amino acid position 28, 30, 31, and/or 93 will be used for enrollment criteria as outlined in inclusion/exclusion.
- **Virologic failure and/or selected follow-up visits**: To better understand the emergence and natural history of RASs in association with virologic failure, samples will be obtained at virologic failure confirmation visits, Follow-up Week (FW) 4, FW12, and FW24. RASs will be assessed for any participant who has detectable virus above 1000 IU/mL and has met an HCV virologic failure criteria. Blood samples for resistance testing are also collected at all visits following confirmation of virologic failure to the end

of the trial. To limit the risk of RASs, participants are not allowed to have monotherapy with EBR or GZR in this protocol.

Participants who have met virologic failure criteria, will be offered follow-up in a 3-year long-term follow-up protocol, MK-5172 Protocol 017, to determine the persistence of RASs and to determine time course of reversion to wild-type.

5.4.2.2 Palatability and Acceptance Assessment Endpoint

Adherence to treatment for chronic HCV infection is necessary for participants to achieve SVR. Palatability may play an important role in adherence to HCV treatment in the pediatric population. Palatability is an important element in the determination of acceptability, and encompasses a product's smell, taste, aftertaste, and texture. Acceptability, including palatability, of EBR/GZR will be assessed in all participants using the Palatability Acceptance Assessment (PAA). In previous studies, the most commonly reported assessment measured palatability preference using a visual analog scale that was modified by including a facial hedonic scale (FHS; facial expression scale depicting various degrees of pleasure) [Thompson, C., et al 2015]. The five-point FHS for taste is one of the most frequently reported types of palatability assessments used in pediatric clinical trials.

5.4.2.3 Safety Endpoints

5.4.2.3.1 General Safety

The safety and tolerability of EBR in combination with GZR are assessed by a clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examinations, and standard laboratory safety tests at appropriate time points as specified in the SoA. Adverse events are graded and recorded according to Section 9.3. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

5.4.2.3.2 Late ALT Elevations and Hepatic ECI Resulting in a Pause in Enrollment

As discussed in Section 3.2.3.2, ALT elevation is a safety signal associated with increased GZR exposures. In this trial, it is expected that the safety profile should match adults. Therefore, safety of an Age Cohort will be based on the following criteria.

If ≥3 participants receiving a given EBR/GZR dose in an Age Cohort experience any of the following, allocation of new participants into the Age Cohort will be paused. Participants that are tolerating treatment with that study drug combination may continue to receive study therapy, but no additional participants will be enrolled until the Sponsor has reviewed all safety and PK data of participants receiving the drug combination.

- ALT or AST increases to >500 IU/L and is confirmed with repeat test immediately.
- ALT or AST increases to >3× baseline and/or nadir, is >100 IU/L, and there is a simultaneous increase in total bilirubin >2× upper limit of normal (ULN) and/or international normalized ratio (INR) is increased from the baseline value and is >1.5 (unless the participant is on anticoagulation).

- ALT or AST increases to >3× baseline and/or nadir, is >100 IU/L, and there is a simultaneous increase in total bilirubin >2× ULN and/or INR is increased from the baseline value and is >1.5 (unless the participant is on anticoagulation).
- The participant's alkaline phosphatase increases to >3× ULN, there is a simultaneous increase in total bilirubin >2× ULN and other causes of elevated alkaline phosphatase are excluded.
- The participant's alkaline phosphatase increases to >5× ULN and other causes of elevated alkaline phosphatase are excluded.
- The participant has a life-threatening clinical or laboratory AE or an AE that results in or prolongs an existing inpatient hospitalization, or death, that is assessed to be study drug-related.

In the event this pause criterion is met, the eDMC will be notified and enrollment into the Age Cohort will be paused and PK-PD analysis will be performed to re-assess and identify an appropriate safety boundary for the pediatric population.

5.4.2.3.3 Growth

Growth assessments will include height and weight measurements of each participant outlined in the SoA. The height of both biological parents will be obtained to determine the participant's growth potential. The participant may continue in the study without these data and/or consent to obtain, use, and disclose parental personal data.

5.4.2.4 Pharmacokinetic Endpoints

The primary PK endpoints for GZR and EBR are steady-state plasma AUC_{0-24}, C_{max}, C_{trough}, and CL/F. Additional steady-state PK parameters such as plasma concentration immediately predose (C_{trough}) and T_{max} will also be estimated.

5.4.2.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

5.4.3 Rationale for the Use of Comparator/Placebo

This is an open-label trial of the safety and efficacy of the combination of EBR and GZR. The current pediatric standard of care is PR. Comparisons will be made to historic efficacy rates and safety profile in pediatric PR clinical trials [Kelly, D. A., et al 2011] [Wirth, S., et al 2010] [McHutchison, J. G., et al 2009].

As discussed in Section 3.2.2.1, the response rates for HCV in children are comparable to response rates in adults. With an all-oral DAA regimen, the medications directly interact with the virus and are not impacted significantly by host response. This is most clearly demonstrated by the minimal impact of race, gender, and IL28B status on efficacy of EBR/GZR in the adult program (see IB). Safety profile will be established without a comparator. PR has a well characterized safety profile in both adults and children.

5.5 Justification for Dose

5.5.1 Starting Dose for This Trial

Mini Age Cohort 1 (aged 12 to less than 18 years) will start with the adult FDC EBR/GZR (50 mg/100 mg) dose. Mini Age Cohort 2 (aged 7 to less than 12 years) is planned to start with the pediatric formulation of EBR/GZR (30 mg/60 mg). Based on the PK analyses from Mini Age Cohort 1 and 2, dosing recommendations will be provided by weight bands for Mini Age Cohort 3 and Expanded Age Cohort 1. Similarly, as described below, dosing regimens for Expanded Age Cohorts 2/3 will be developed based on the population PK model and dosing recommendations will be provided by weight bands. Weight bands for Mini Age Cohort 3 and the Expanded Age Cohorts will be determined by PK analyses. See Section 7.1 for a description of EBR/GZR adult FDC dose versus the pediatric formulation.

5.5.1.1 Dose Justifications

Since the relationship between exposure and safety and efficacy is well-established for EBR and GZR in adults, achieving AUC exposures in pediatric patients that is similar to adults is anticipated to result in similar safety and efficacy profile as adults. Therefore, the target dose in each pediatric age group is one that yields AUC exposures similar to that obtained in adults who receive EBR (50 mg) and GZR (100 mg).

Similarity between pediatric and adult AUC will be assessed based on the GM AUC values. The pediatric GM AUC should be approximately within 2-fold that estimated in adults for EBR and GZR. Additionally, the pediatric GM AUC range should fall within the defined clinical bounds for EBR [0.5, 2.0] and GZR [0.4, 5.0]. Therefore, the pediatric GM AUC for each age group should fall within ~0.81-8.6 μM*hr for GZR and ~1.1-4.4 μM*hr for EBR, which corresponds to the AUC associated with the lower and upper clinical bounds. Otherwise, the dose will be adjusted for the Expanded Age Cohorts so that the AUC falls within the clinical bounds.

For EBR and GZR, CYP3A, P-gp, and OATP1B1/3 are the known enzymes/transporters to consider when thinking about potential age-related PK changes in the pediatric population. Children >7 years of age have mature CYP3A enzymes that are comparable to those of adults [Ince, I., et al 2013], with minor incremental maturation of CYP3A in children 3-7 years of

age [Johnson, T. N., et al 2006]. OATP1B1 protein expression is not age dependent in the range of 9 days to 12 years [Thomson, M. M., et al 2016], or in the range of 7 to 70 years [Prasad, B., et al 2014], and OATP1B3 protein expression was also not age dependent in the range of 2 to 12 years [Thomson, M. M., et al 2016]. These observations indicate that minimal to no age-related changes related to enzyme/transporter expression or maturation for EBR and GZR are anticipated in the age range of 3-18 years compared to adults.

5.5.1.2 Dose in Mini Age Cohort 1 and 2

The adult Phase II/III clinical program included patients with body weight down to 37 kg, who demonstrated favorable PK, safety, and efficacy. Based on the comparable body weight and CYP3A and OATP1B maturation in participants aged 12 years up to 18 years, participants in Mini Cohort 1 will be administered the adult FDC dose of EBR/GZR (50 mg/100 mg), which is anticipated to result in comparable exposures to adults.

The EBR and GZR PBPK models developed for the adult program were used to estimate exposures in pediatric HCV patients from 12 to 18 years of age. The pediatric simulations assumed the same OATP1B/3 factor for hepatic uptake as estimated for adult patients. The simCYP^{TM} program used for the PBPK model accounts effects of physiology (eg, body weight, liver size) age-related CYP3A abundance, and HCV infection in these pediatric participants on PK. The PBPK model suggests that the adult dose of EBR/GZR (50 mg/100 mg) would result in comparable plasma exposures in 12-18 year olds as in adults.

The EBR and GZR PBPK models were also used to estimate exposures in pediatric HCV patients from 7 to 12 years of age. A dose of 30 mg and 60 mg for EBR and GZR, respectively, in pediatric HCV patients from 7 to 12 years of age is estimated to result in comparable AUC exposures as adult HCV patients that are administered the FDC. The starting dose for Mini Age Cohort 2 may be refined, if needed, based on the estimated Day 1 AUC from Mini Age Cohort 1.

5.5.1.3 Dose in Mini Age Cohort 3 and Expanded Age Cohorts 1, 2, and 3

The doses in these cohorts will be determined based on cumulative pediatric PK data and population PK and PBPK modeling and simulation. The Day 1 and TW4 PK data from Mini Age Cohorts 1 and 2 will be used to estimate the AUC for these participants and will be incorporated in the population PK and PBPK models.

The models will then be used to estimate the anticipated exposure and select optimal doses for Mini Age Cohort 3 and Expanded Age Cohort 1. PK data from these cohorts will in turn be used to update the model, and select the dose for Expanded Age Cohort 2/3. Dosing recommendations for Mini Age Cohort 3 and the Expanded Age Cohorts will be provided by weight bands, which will be determined by PK analyses. At each step, the goal of model-based simulations will be to derive a dosing regimen expected to provide similar exposures in pediatric patients as in adults.

5.5.2 Maximum Dose/Exposure for This Trial

The maximum dose in this trial will not exceed EBR 50 mg and GZR 100 mg.

6. Study Population

Male/Female participants with chronic hepatitis C GT1 or GT4 virus infection from the age of 3 years up to <18 years will be enrolled in this trial.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. The participant has HCV RNA (≥1,000 IU/mL in peripheral blood) at the time of screening.
2. The participant has documented chronic HCV GT1 or GT4 infection as follows:
    a) positive for anti-HCV antibody, HCV RNA, or HCV GT1 or GT4 at least 6 months before Day 1; or
    b) positive for anti-HCV antibody or HCV RNA with a liver biopsy consistent with chronic HCV infection (such as the presence of fibrosis) before Day 1.
3. For participants with GT4, HCV RNA <800,000 IU/mL at the time of screening.
4. For participants with GT1a, no evidence of NS5A RASs detected at screening at positions 28, 30, 31, and/or 93.
5. The participant has liver disease staging assessment as follows:
    a) Absence of cirrhosis (F0 to F3) defined as any one of the following:
        i. Liver biopsy performed within 24 months of Day 1 showing absence of cirrhosis, or
        ii. FibroScan® performed within 12 months of Day 1 with a result ≤12.5 kPa (only for participants aged 12 years up to 18 years), or
        iii. In the absence of criterion i. or ii. above, absence of cirrhosis can be determined by the investigator according to local clinical standards that includes physical examination during screening in combination with laboratory evaluation during screening and/or imaging test within 6 months of screening.
    b) Compensated Cirrhosis (F4) defined as any one of the following:
        i. Liver biopsy performed prior to Day 1 showing cirrhosis, or
        ii. FibroScan® performed within 12 months of Day 1 with a result >12.5 kPa (only for participants aged 12 years up to 18 years), or

iii. In the absence of criterion i. or ii. above, cirrhosis can be determined by the investigator according to local clinical standards that includes physical examination during screening in combination with historical or current laboratory evaluation and/or imaging with findings consistent with cirrhosis (such as firm or enlarged liver, splenomegaly).

NOTE: Enrollment in the Mini Age Cohorts will be limited to non-cirrhotic participants.

6. The participant has an HCV treatment status that is one of the following:
   a) GT1 and GT4: HCV TN (defined as no prior exposure to any interferon [IFN]-containing regimen, RBV, or other HCV-specific DAA agent).
   b) GT1 only: HCV TE (defined as prior virologic failure during or after treatment with an IFN or pegylated-IFN with or without RBV; or intolerance to IFN or pegylated-IFN with or without RBV). Participants cannot have previously received treatment with HCV specific DAA agents (**NOTE**: GT4-infected participants cannot be HCV TE).

Demographics

7. The participant is male or female between 3 years to less than 18 years of age on day of signing informed consent/assent.
8. For participants in the Mini Age Cohorts only (these restrictions do not apply for the Expanded Age Cohorts):
   a) Weight:
      i. Age Cohort 1: ≥32 kg
      ii. Age Cohort 2: ≥19 kg
      iii. Age Cohort 3: ≥12 kg
   b) Race: Participants of non-Asian Race.

Female participants:

9. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 14 days after the last dose of study treatment.

Informed Consent/Assent

10. The participant's legally acceptable representative(s) provides written informed consent for the study and, when applicable, the participant provides written informed assent.

    NOTE: The participant's legally acceptable representative(s) may also provide consent for Future Biomedical Research (FBR); however, the participant may participate in the main study without participating in FBR.

Other Inclusion Criterion

11. The participant must be able to swallow the placebo to EBR/GZR (FDC) prior to allocation. This is applicable only to participants in Mini Age Cohort 1 and, if it is determined by PK analysis that Expanded Age Cohort 1 will also receive the adult FDC dose, to participants in Expanded Age Cohort 1.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. The participant has evidence of decompensated liver disease manifested by the presence of or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs or symptoms of advanced liver disease.
2. The participant is cirrhotic AND has a Child-Turcotte-Pugh score >6, corresponding to a Child Class B or C.

   NOTE: To calculate the Child-Turcotte-Pugh score and classification, refer to the following website: http://www.mdcalc.com/child-pugh-score-cirrhosis-mortality/.

   NOTE: For participants with documented Gilbert's syndrome, use +1 for the bilirubin category of the Child-Pugh calculation.
3. The participant is co-infected with HIV.
4. Has evidence of past or present hepatitis B infection (either hepatitis B core antibody [anti-HBc] positive and/or hepatitis B surface antigen [HBsAg] positive) at screening.
5. The participant has a history of malignancy ≤5 years prior to signing informed consent or is under evaluation for other active or suspected malignancy including HCC.
6. A WOCBP is expecting to conceive or donate eggs from Day 1 through at least 14 days after the last dose of study treatment or longer if dictated by local regulations.
7. The participant has any of the following conditions:
   a) organ transplants (including hematopoietic stem cell transplants) other than cornea and hair.
   b) poor venous access that precludes routine peripheral blood sampling required for this study.

c) history of gastric surgery (eg, stapling, bypass) or malabsorption disorders (eg, uncontrolled celiac sprue disease).

d) any clinically significant cardiac abnormalities/dysfunction that may interfere with participant treatment, assessment, or compliance with the protocol, including but not limited to: unstable angina, unstable congestive heart failure, unstable arrhythmia; participants currently under evaluation for a potentially clinically significant cardiac abnormality/dysfunction are also excluded.

e) any major medical condition, clinically significant illness (other than HCV), pre study laboratory or electrocardiogram (ECG) abnormality, or history of any illness, including failure to thrive, which, in the opinion of the investigator, might interfere with participant treatment, assessment, compliance with the protocol, or confound the results of the study or pose additional risk in administering the study drug to the participant.

f) history of a medical/surgical condition that resulted in hospitalization within the 3 months prior to enrollment, other than for minor elective procedures.

g) medical/surgical conditions that may result in a need for hospitalization during the study duration.

NOTE: Elective procedures will be permitted following 14 days after taking the last dose of study drug.

h) any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids, tumor necrosis factor antagonists, or other immunosuppressant drugs through FW24.

i) life-threatening serious adverse event (SAE) during the screening period.

j) Evidence of history of chronic hepatitis not caused by HCV, including but not limited to, drug-induced hepatitis, hemochromatosis, Wilson's disease, α1 antitrypsin deficiency, alcoholic liver disease, and autoimmune hepatitis (See Exclusion Criterion #4 regarding evidence of history of hepatitis B).

NOTE: Participants with history of acute non-HCV-related hepatitis, which resolved >6 months before study entry, can be enrolled.

8. A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study treatment (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Prior/Concomitant Therapy

9. The participant is taking or plans to take any of the prohibited medications listed in the protocol (see Section 7.7 – Concomitant Therapy) or is taking herbal supplements, including but not limited to St. John's Wort (Hypericum perforatum), from 2 weeks prior to Day 1 through 2 weeks after the study treatment period.

NOTE: For the Mini Age Cohorts only, the participant is taking or plans to take methadone or strong CYP3A inhibitors.

10. The participant has had previous HCV DAA treatment.

Prior/Concurrent Clinical Study Experience

11. The participant is currently participating or has participated in a study with an investigational compound within 30 days of signing informed consent/assent and is not willing to refrain from participating in another such study through 24 weeks after the study treatment period (FW24).

Diagnostic assessments

12. The participant has exclusionary laboratory values at the screening visit as listed in Table 4 below.

    NOTE: If any of the laboratory exclusion criteria below in Table 4 are met, the site may have the abnormal value retested one time.

Table 4 Laboratory Exclusion Criteria

Laboratory Assessment	Exclusionary Values
Creatinine clearance (eGFR)[a]	<50 mL/min/1.73 m^2
Hemoglobin	<10 g/dL
Platelets	<100 × 10^3/µL
Serum Albumin	<3.0 g/dL
INR	>1.7 (unless participant has a stable INR on an anticoagulant regimen)
ALT	>10 × ULN
AST	>10 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; ULN = upper limit of normal

[a] Creatinine clearance will be evaluated as eGFR based on the modification of diet in renal disease equation:

$eGFR\ (mL/min/1.73\ m^2) = 175 \times (Scr, std)^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ black)$

Scr, std: serum creatinine measured with a standardized assay

Other Exclusions

13. The participant has significant emotional problems or a clinically significant psychiatric disorder that may interfere with participant treatment, assessment, or compliance with the protocol.
14. The participant has clinically relevant drug or alcohol abuse within 12 months of screening that may interfere with participant treatment, assessment, or compliance with the protocol.
15. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this study.

6.3 Lifestyle Restrictions

Based on the number of PK sampling timepoints, an overnight stay in the clinic is recommended for the Day 1 (Mini Age Cohort 1 only) and Week 4 visits (all participants).

6.3.1 Meals and Dietary Restrictions

EBR/GZR (FDC) can be taken without regard to food; however, intake of EBR/GZR pediatric formulation must be mixed in a soft food dosing vehicle (applesauce, pudding, or yogurt).

6.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

If a participant discontinues from trial treatment prior to intensive PK sampling at TW4, a replacement participant may be enrolled if deemed appropriate by the Sponsor. The replacement participant will be matched to the same cohort and receive the same treatment as the participant being replaced. The replacement participant will be assigned a unique treatment/allocation number. The trial site should contact the Sponsor for the replacement participant's treatment/allocation number.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatments to be used in this trial are outlined below in Table 5.

Table 5 Study Treatments

Study Treatment Name:	EBR/GZR FDC	Placebo to match MK-5172A (EBR/GZR) FDC*	MK-8742 (EBR) Pediatric Formulation	MK-5172 (GZR) Pediatric Formulation
Dosage Formulation:	Tablet	Tablet	Oral granules***	Oral granules***
Unit Dose Strength(s):	50 mg/100 mg	0 mg/0 mg	0.5 mg	1 mg
Dosage Level(s):	1 tablet QD	1 tablet given prior to allocation**	TBD – dose will not exceed 50 mg	TBD – dose will not exceed 100 mg
Route of Administration:	Oral	Oral	Oral	Oral
Sourcing:	Sponsor	Sponsor	Sponsor	Sponsor

*Placebo tablets are different in color but identical in size and shape to the active EBR/GZR FDC tablets.

**Placebo to EBR/GZR (FDC) tablet is given once prior to allocation to participants in Mini Age Cohort 1. This will also apply to participants in Expanded Age Cohort 1 if it is determined by PK analysis that Expanded Age Cohort 1 will also receive the adult FDC dose.

***Pediatric formulation supplied as single entity packets.

EBR = elbasvir; FDC = fixed dose combination; GZR = grazoprevir; PK = pharmacokinetics; QD = once-daily; TBD = to be determined.

As PK data becomes available, the dose proposed for participants will be adjusted to meet the scientific goals and study objectives.

Mini Age Cohort 1 will be administered FDC tablets (EBR 50 mg/GZR 100 mg). Expanded Age Cohort 1 is expected to receive FDC tablets but alternatively may receive pediatric formulation, if PK data suggests a lower dose (dosage to be informed by trial). Age Cohorts 2 and 3 will be administered pediatric formulation product (dosage to be informed by trial). Following assignment of formulation, participants may not change from FDC tablets to pediatric formulation or from pediatric formulation to FDC tablets during the course of the trial.

The pediatric formulation in this study allows for flexibility of dosing. EBR 0.5 mg and GZR 1.0 mg are packaged as single entity packets, which contain oral granules. The foil packets are opened and the contents (oral granules) are mixed into a soft food vehicle (applesauce, pudding, or yogurt) prior to consumption.

Each single entity packet is individually labeled with the Sponsor's product number (MK-8742 is EBR; MK-5172 is GZR) and contains 10 oral granules of either EBR or GZR.

- EBR packets have 5 mg per unit package and
- GZR packets have 10 mg per unit package

The recommended dosing for each Age Cohort will be detailed by the Sponsor in a memo to the Study File. Dosing recommendations for Mini Age Cohort 3 and all Expanded Age Cohort(s) will be by weight bands, which will be determined based on PK analyses. This memo will be communicated to the site personnel. The memo should be forwarded to the Institutional Review Board/Ethics Review Committee (IRB/ERC) by the Investigator, as appropriate per IRB/ERC guidelines.

All placebos were created by the Sponsor to match the active product.

All supplies indicated in Table 5 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

7.2 Dose Modification (Escalation/Titration/Other)

Dose modification of EBR/GZR is not permitted by the site personnel. For more information on dose modification during the course of the trial, see Section 5.5.1.1.

7.3 Method of Treatment Assignment

Participants will be allocated to treatment via an interactive voice response system/interactive web response system (IVRS/IWRS) by non-random assignment.

7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

By design, participants will be stratified by Age Cohorts (3 years to <7 years, 7 years to <12 years, 12 years to <18 years).

7.4 Blinding

This is an open-label trial; therefore, the Sponsor, investigator and participant will know the treatment administered.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The study is designed with staged enrollment. PK data from earlier enrolled cohorts within the study will inform the recommended daily dose of EBR and GZR for subsequently enrolled cohorts. Details are provided in Section 5.5 – Justification for Dose.

Once the Sponsor has determined and communicated recommended dosing for subsequent cohorts receiving the pediatric formulation of EBR/GZR, site personnel will count and package the appropriate number of EBR and GZR single entity packets for each participant's daily dose. Daily dosage preparation will be multiples of individually labeled unopened packets.

7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

The participant/legally acceptable representative will be provided a Study Medication and Meal Diary (SMD) to record the number of FDC tablets or EBR/GZR pediatric formulation packets taken during the treatment period (Section 9.11.2). At all visits during the treatment period, site personnel must verify the accuracy of the dosing SMD by comparing entries with amounts of unused study medication. If a discrepancy is noted, investigator/study coordinator must discuss the discrepancy with the participant/legally acceptable representative and the explanation must be documented.

Administration of trial medication will be witnessed by the investigator and/or trial staff at the Day 1, TW4, and TW8 (visits where the predose PK samples will be collected).

Missed Doses

If a participant misses a dose (or any part thereof) of EBR/GZR, the next dose should not be doubled in order to compensate for what has been missed. The participant should be instructed as follows:

- If the next dose is in more than 8 hours, the missed dose should be taken as soon as possible and the normal dosing schedule resumed.

- If the next dose is less than 8 hours, the missed dose should be skipped and the normal dosing schedule resumed.

Treatment Interruptions

Treatment interruptions should be avoided, but if for any reason EBR/GZR needs to be interrupted, it can be interrupted for up to 3 consecutive days.

Interruptions from the protocol specified treatment for >3 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.7 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the dosing period. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant or the participant's legally acceptable representative.

It is important for investigators to review each medication (prescription and non-prescription) the participant is taking before starting the study and at each study visit.

- All concomitant medications should be reviewed and data collected through 2 weeks after the study treatment period. Participants or the participant's legally acceptable representative should be asked about any new drugs/vaccines they are taking/have taken or changes to any previously reported drugs/vaccines.
    - Drugs known to be hepatotoxic (ie, drugs with a warning of hepatotoxicity in the package insert) should be avoided. Investigators are encouraged to review each medication for potential hepatotoxicity using the website www.livertox.nih.gov.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.
- Non-study HCV medications/therapies, including IFN, are prohibited through FW24. Any use should be reported throughout the study duration.

Prohibited Medication

Specific restrictions for concomitant therapy are listed in Table 6. The medications/therapies are not permitted during the dosing period and for 14 days thereafter.

Table 6 List of Prohibited Medications

Known hepatotoxic drugs	Etifoxine, isoniazid, nitrofurantoin, phenytoin, oral ketoconazole
Herbal supplements	Including, but not limited to: St. John's wort
Strong and moderate CYP3A/P-gp inducers, including but not limited to	Anti-infectives: nafcillin, rifampin Anticonvulsants: carbamazepine, phenytoin, phenobarbital Endothelin antagonists: bosentan Wakefulness-promoting agents: modafinil Herbal products: St. John's wort HIV medications: efavirenz, etravirine
OATP inhibitors	Immunosuppressants: cyclosporine Anti-infectives: rifampin HIV medications: atazanavir, darunavir, lopinavir, saquinavir, tipranavir
HCV medications	All non-study HCV medications/therapies
HIV medications, including but not limited to	All boosted and unboosted HIV protease inhibitors including, but not limited to: atazanavir, darunavir, lopinavir, saquinavir, tipranavir Cobicistat-containing regimens: elvitegravir/cobicistat/emtricitabine/tenofovir (disoproxil fumarate or alafenamide) efavirenz etravirine
HMG-CoA reductase inhibitors (statins)	*All statins are prohibited during the dosing period of the study*
Investigational agents	All investigational agents (aside from study-related therapies)
Systemic corticosteroids	Systemic corticosteroid use for more than 2 weeks (except pulmonary/nasal administration)
AE=adverse event; CYP3A/P-gp=cytochrome P4503A/P-glycoprotein; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HMG-CoA=3-hydroxy-3-methylglutaryl-coenzyme A; OATP=organic anion-transporting polypeptide.	

In addition to the medications listed in Table 6, participants in the Mini Age Cohorts are prohibited from taking the following medications:

- Strong CYP3A inhibitors: Including but not limited to, clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone
- Methadone

Allowed Medications

Table 7 List of Allowed Medications

Commonly Used for the Pediatric Population	
Hypoglycemic agents	Insulin, sitagliptin, glipizide, metformin
Contraceptives	Oral contraceptive pills, progesterone injects, intrauterine devices
Antidepressants/anxiolytics	Citalopram, paroxetine, duloxetine, escitalopram, fluoxetine, bupropion, trazodone, diazepam, clonazepam, temazepam, lorazepam
Acid reflux	Acid blockers: H_2 blockers and proton pump inhibitors
Asthma	histamine blockers, inhaled/nasal corticosteroids, montelukast
Less Commonly Used for the Pediatric Population	
Anti-coagulants	Warfarin, heparin, low molecular weight heparin, aspirin, fondaparinux, desirudin, acenocoumarol
Antihypertensives	Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: enalapril, captopril, lisinopril, ramipril, valsartan, losartan, telmisartan Beta blockers: atenolol, metoprolol, propranolol (for other beta blockers, please consult with the Sponsor*)* Calcium-channel blockers: amlodipine, diltiazem, verapamil (for other calcium-channel blockers, please consult with the Sponsor) Hydralazine, clonidine, minoxidil, isosorbide nitrates
Anemia	Erythropoietin
Diuretics	Hydrochlorothiazide, furosemide, spironolactone, triamterene
Opiate substitution therapy	Buprenorphine/naloxone, methadone **Note**: Participants in the Mini Age Cohorts are prohibited from taking methadone
Immunosuppressants	Prednisone, daily doses <10 mg or a short course lasting <2 weeks for higher doses.

Given that the lists above are not comprehensive, the investigator should use his/her medical judgment when a participant presents with a medication not on the list and consult with the Sponsor.

Concomitant medications and therapies discontinued during the dosing period may be restarted 2 weeks after the last dose of study drug is administered and may continue during the follow-up period.

7.7.1 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.9 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant/legally acceptable representative, the trial site personnel, the Sponsor and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - SoA and Section 9.11.4 – Discontinued Participants Continuing to be Monitored in the Study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- Participant meets any HCV virologic failure criteria (see Section 5.4.2.1.1).
- The participant has a confirmed positive serum pregnancy test.
- A physician feels it is in the best interest of the participant to discontinue.
- ALT or AST increases to >500 IU/L and is confirmed with repeat test immediately.
- ALT or AST increases to >3× baseline and/or nadir, is >100 IU/L, and there is a simultaneous increase in total bilirubin >2× ULN and/or INR is increased from the baseline value and is >1.5 (unless the participant is on anticoagulation).
- Alkaline phosphatase increases to >3× ULN, there is a simultaneous increase in total bilirubin >2× ULN, and other causes of elevated alkaline phosphatase are excluded.

- Alkaline phosphatase increases to >5× ULN and other causes of elevated alkaline phosphatase are excluded.
- The participant has a life-threatening clinical or laboratory AE or an event that results in or prolongs an existing inpatient hospitalization that is assessed to be a study drug-related laboratory or clinical AE.

A participant **may** be discontinued from treatment but continue to be monitored in the study for any of the following reasons:

- SAE assessed by the physician investigator as possibly or probably related to study medication. Investigator may continue the participant in the trial, if it is deemed to be in the best interest of the participant to stay on the study treatment.
- Failure to comply with the dosing, evaluations, or other requirements of the trial.

For participants who are discontinued from study treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the SoA, should be completed.

Participants may be allowed to begin study treatment again if deemed medically appropriate, upon consultation with the Sponsor.

8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study including the procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9 – Withdrawal/Discontinuation.

8.3 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant/legally acceptable representative, the following procedures are to be performed:

- The site must attempt to contact the participant/legally acceptable representative and reschedule the missed visit. If the participant/legally acceptable representative is contacted, the participant/legally acceptable representative should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant/legally acceptable representative at each missed visit (eg, phone calls and/or a certified letter to the participant's/legally acceptable representative's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of trial site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant or the participant's legally acceptable representative. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The amount of blood collected from each participant over the duration of the study is approximately 126 mL for participants in Age Cohort 1 and 119 mL for participants in Age Cohorts 2 and 3. Details regarding specific laboratory assessments/procedures to be performed in this study, including approximate blood volumes drawn by visit and by sample type per participant, can be found in Appendix 2.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Administrative and General Procedures

9.1.1 Informed Consent/Assent

The investigator or qualified designee must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent/assent is in place.

9.1.1.1 General Informed Consent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the participant/legally acceptable representative before participation in the trial.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form and any written information provided to the participant/legally acceptable representative must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's/legally acceptable representative's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent/assent to the participant or the participant's legally acceptable representative, answer all of his/her questions, and obtain written informed consent/assent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent/assent will be given to the participant or the participant's legally acceptable representative.

9.1.1.3 Parental Consent to Use and Disclose Personal Data

Appropriate written consent must be obtained prior to collecting and disclosing the height(s) of the biological mother and father of the subject. It is the responsibility of the investigator/IRB/IEC to ensure the appropriate consent is obtained according to local law and IRB/IEC guidelines. The consent form must be approved by the IRB/IEC. The consent may be obtained anytime during the study. If biological parents are unable to be reached or the biological parents do not provide consent to use and disclose his/her personal data, the participant may continue in the study.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

9.1.3 Participant Identification Card

All participants or their legally acceptable representative will be given a Participant Identification Card identifying them as participants in a research study. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant or their legally acceptable representative with a Participant Identification Card immediately after the participant or their legally acceptable representative provides written informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

A medical history (including any drug allergies, eg, sulfa allergies) will be obtained by the investigator or qualified designee.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before starting the trial.

9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant through 2 weeks after the study treatment period. Non-study HCV medications/therapies are prohibited through FW24; any use should be reported throughout the study duration.

The investigator or qualified designee will discuss with the participant specific restrictions for concomitant medications per Section 7.7 – Concomitant Therapy.

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to treatment allocation. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.11.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

9.1.8 Treatment Administration

Participants in Mini Age Cohort 1 must be able to demonstrate the ability to swallow the adult FDC placebo tablet in order to be eligible for the trial. Prior to allocation, administration of the placebo to EBR/GZR FDC tablet will be witnessed by the investigator and/or study staff to participants who have met all other eligibility criteria for allocation into Mini Age Cohort 1. If it is determined by PK analysis that Expanded Age Cohort 1 will also receive the adult FDC dose, administration of the placebo FDC tablet will be witnessed by the investigator and/or study staff to participants in Expanded Age Cohort 1. Participants in this Age Cohort that cannot swallow the placebo FDC tablet are not eligible to be allocated into the trial.

Following completion of the Day 1 procedures per SoA (Section 2) and confirmation of eligibility, the site pharmacist or study coordinator will contact the IVRS/IWRS for treatment allocation.

NOTE: Sites should not call IVRS/IWRS for treatment assignment until the participant has met all criteria for the study and are ready to receive the first dose of study medication on Day 1.

Administration of the following doses will be witnessed by the investigator and/or study staff during the site visit:

- First dose of study medication at Day 1 for all participants.
- TW4
- TW8

All other dosing will be performed by the participant/legally responsible representative (ie, unsupervised at his/her home) and recorded on the participant's SMD.

9.1.8.1 Timing of Dose Administration

Participants will be instructed to take study medication at approximately the same time each day. EBR/GZR (FDC) can be taken without regard to food; however, intake of EBR/GZR pediatric formulation must be mixed in a soft food dosing vehicle (applesauce, pudding, or yogurt).

If a participant vomits a dose within 30 minutes of ingestion, the full dose can be repeated one time. If a participant vomits and it has been longer than 30 minutes from the time of ingestion, the dose should not be repeated. Take the next dose at the usual time.

9.1.9 Withdrawal/Discontinuation

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.9.1 Withdrawal From Future Biomedical Research

A Participant's consent for Future Biomedical Research may be withdrawn by the participant or the participant's legally acceptable representative (as appropriate) and their specimens and all derivatives destroyed. A participant's consent may be withdrawn at any time by contacting the principal investigator for the main study. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

9.1.10 Participant Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

9.1.11 Domiciling

Participants will report to the clinical research unit on the morning of intensive PK sampling visits. Participants are recommended to remain in the unit until 24 hours post-dose.

9.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

9.2 Efficacy Assessments

9.2.1 HCV RNA Measurements

Specimens must be obtained from all participants for the following HCV efficacy measurements:

- HCV GT on baseline sample (for trial entry) using the Food and Drug Administration (FDA) approved Abbott HCV Real Time Genotype II assay which detects HCV GT 1a, 1b, 2, 3, 4, 5, and 6 through the use of GT-specific fluorescent-labeled oligonucleotide probes in a real-time reverse transcription polymerase chain reaction (RT-PCR) assay. The RT-PCR reaction uses 3 sets of HCV specific amplification primers targeting the 5' untranslated region (for all GTs) and NS5B regions from GT1a and 1b. The assay has accuracy of >96% for GT1, 1a, 1b, 2, 3 and 5, 89% for GT5 and 83% for GT6 with 100% specificity in HCV serologically negative plasma samples. Phylogenetic analyses will be performed using sequences for NS3, NS5A, and NS5B regions to ensure accurate assignment of sample GT/subtype.
- HCV RNA plasma levels at various time points per the SoA (Section 2). HCV RNA in plasma will be measured using a COBAS® AmpliPrep/COBAS® Taqman® HCV Test, v2.0® assay with a LLOQ of 15 IU/mL. Results from the sample collected at the screening visit are used to determine eligibility. Samples collected at other time points, after Day 1, are used for efficacy analyses and to identify participants who meet virologic failure criteria. Leftover plasma may be used for viral resistance testing if needed.

9.2.2 Viral Resistance Measurements

Specimens will be obtained from participants for HCV viral resistance measurements:

- Blood will be drawn from all subjects at screening to assess viral resistance.
- Viral resistance testing will be performed for all participants to determine pre-existing RASs to EBR and GZR. Next-generation sequencing will be performed with a 15% sensitivity threshold. Additional resistance testing on these samples may be performed.

  - The results of this test will be used for screening criteria in GT1a-infected participants. See Section 6.1 for specific criteria for GT1a-infected participants.

- Blood samples for resistance testing are also collected at follow-up visits and at the virologic failure confirmation visit (should this occur) for genotypic and investigational assays to assess emergence of resistance to the components of EBR/GZR following treatment initiation.
- Leftover plasma may be used for FBR only if the participant/legally acceptable representative signed for FBR consent.

9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 8.

Table 8 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event		**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period**	**Reporting Time Period: After the Protocol Specified Follow-up Period**		**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - subject is receiving placebo run-in or other run-in treatment	Report all	Not required		Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose		Report if: - due to protocol-specified intervention - causes exclusion - subject is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)		Within 24 hours of learning of event
Pregnancy/Lactation Exposure		Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome		Within 24 hours of learning of event
Event of Clinical Interest		Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting <u>OR</u> - Overdose of Sponsor's product that is not associated with clinical symptoms or abnormal laboratory results	Not required		Within 24 hours of learning of event

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and non-leading verbal questioning of the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) is the preferred method to inquire about AE occurrence.

9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

There are no protocol-specific exceptions to the AE experience reporting presented in Section 9.3.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. first instance of ALT or AST >500 IU/L after initiation of study therapy through 14 days following treatment.*

3. first instance of ALT or AST >3x nadir AND >100 IU/L after initiation of study therapy through 14 days following treatment.*

*Note: The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require and additional evaluation for an underlying etiology. The trial site guidance for assessment and the follow up of these criteria can be found in the Investigator Trial File Binders (or equivalent).

Reporting requirements for ECIs are presented in Table 8. Any ECI involving overdose or ALT/AST criteria are to be reported to the Sponsor within 24 hours.

9.4 Treatment of Overdose

In this trial, an overdose is any dose higher than the prescribed dose of EBR/GZR.

- FDC: 1 tablet once daily
- Pediatric Formulation: Dosage communicated (TBD as informed by PK Modeling)

No specific treatment is recommended for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this trial are provided below.

Clinically significant findings from any safety assessments conducted prior to starting study therapy (eg, physical examinations, vital signs, and ECGs at screening) should be captured in the Medical History electronic case report form (eCRF). For safety assessments performed during study treatment or follow-up, any clinically significant changes compared with the assessments prior to study treatment must be captured as AEs. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

Planned time points for all safety assessments are provided in the SoA.

9.5.1 Physical Examinations

All physical examinations must be conducted as per institutional standard by the principal investigator or subinvestigator (physician, physician assistant, or nurse practitioner) as follows:

- A complete physical examination at screening and Day 1 to include the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic examinations should be performed when clinically indicated.
- A focused physical examination at any other visit when clinically indicated.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height and weight will be measured and recorded per the SoA and used by the Sponsor to calculate body mass index.

9.5.1.1 Height of Biological Parent(s)

The height of the biological parents will be collected between screening and Day 1. If biological parents are unable to be reached during that period the participant may continue in the trial. Later attempts during the trial will be made to collect these data. Biological parental consent must be signed prior to obtaining, using, and disclosing their personal data.

Every effort should be made to measure the height of both biological parents at the study site. If this is not feasible for some parents, a self-reported height will be acceptable. The participant may participate in the study without these data and/or consent to obtain, use, and disclose parental personal data.

9.5.2 Vital Signs

- Vital signs will be measured in a semi-recumbent position after 10 minutes rest and will include oral temperature, systolic and diastolic blood pressure, and heart rate.
- NOTE: Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, or axillary temperatures may be taken.

9.5.3 Electrocardiograms

- Special care must be taken for proper lead placement and participants should be shaved as necessary. Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained.

9.5.4 Date of Menarche

The date of menarche must be recorded for females who have previously experienced menarche. Once a date of menarche has been confirmed, the participant is considered to be a WOCBP. For prepubescent females, site staff should continue to review and record, as appropriate, at each visit during the treatment period.

9.5.5 Contraception Confirmation

Throughout the screening and treatment periods, precaution must be taken to avoid pregnancy in WOCBP. Confirmation must be obtained and documented by site personnel that WOCBP are using acceptable methods of contraception (see Appendix 5). This assessment must be documented in the participant's study chart at each specified visit.

9.5.6 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

9.5.6.1 Fibroscan®

This method for assessing liver cirrhosis has gained increasing acceptance. In the US, this methodology is FDA-approved and in other countries, it is often the preferred method of assessment. FibroScan® results are influenced by a number of confounders including ALT, ascites, and underlying disease. Hepatitis C is one of the best studied and is the disease state with the most reproducible/reliable results. FibroScan® has been evaluated in many liver diseases for the staging of liver fibrosis, and has been demonstrated to be very effective for differentiating cirrhosis (F4) from no cirrhosis (<F4), but it is less capable of differentiating gradations of fibrosis. In a large study by Castera et al. [Castera, L., et al 2008], in a population of participants with chronic HCV infection, a cut-off of 12.5 kPa was selected for

cirrhotics. At this cut-off, the sensitivity and specificity of the test for cirrhosis were 87% and 91%, respectively, and the negative predictive value was 95%. Since this analysis was assessed specifically in participants with chronic HCV infection, the cut-off value >12.5 kPa used by Castera was selected to include cirrhotics in the current study.

9.5.6.2 Pregnancy Testing

For WOCBP (see Appendix 5), a urine pregnancy test must be performed at the site on Day 1, with negative results prior to initiating study treatment. If the urine pregnancy test result is positive, a serum pregnancy test will be performed. If the result of the serum pregnancy test is positive, the participant must be excluded from the study per Section 6.1 – Inclusion Criteria.

Ongoing pregnancy testing will be conducted per the SoA. If the participant has a confirmed positive serum pregnancy test, study treatment must be discontinued per Section 8.1 – Discontinuation/Withdrawal Criteria and the pregnancy reported per Section 9.3.6 – Pregnancy and Exposure During Breastfeeding.

9.5.6.3 HIV Evaluation

HIV serology samples will be collected and processed for all participants at screening.

9.5.6.4 Hepatitis B Virus Evaluation

Samples will be collected from each participant to assess HBsAg and anti-HBc, at screening.

9.6 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK will be collaboratively determined by the department of Quantitative Pharmacology and Pharmacometrics and the appropriate department within Clinical Research. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional PD markers.

PK samples will be collected in all pediatric participants. The proposed PK sampling scheme across all age groups is provided below in Table 9.

9.6.1 Blood Collection for Plasma EBR/GZR

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

Pharmacokinetic samples will be collected according to the PK sampling schemes shown in Table 9. To avoid multiple venipunctures in pediatric participants, sites are encouraged to use a peripheral venous access port to collect multiple blood samples for intensive PK sampling. More details on this procedure for blood collection are provided in the Laboratory Manual.

On all PK visits where a predose sample will be collected, the visit should occur prior to the participant's regular time for taking their study medication and the participant should withhold their dose until after the visit. For predose PK visits (ie, Day 1, Week 4, Week 8), if it is not feasible to schedule the visit prior to the participant's regular time for taking their

study medication, the participant should withhold their dose until reporting to the clinic. The predose PK sample will be obtained and the dose will be administered at the clinic. The date and time of each PK sample as well as the date and time of the last dose of EBR/GZR prior to the PK sample will be recorded.

All PK samples will be used to evaluate PK exposures, and potentially also the PK-efficacy and PK-AE relationships of EBR and GZR. The date and time of each PK sample as well as the date and time of the last dose of EBR/GZR prior to the PK sample will be recorded.

The PK sampling schemes selected for Day 1 and TW4 facilitates the ability to estimate all PK parameters specified in the objectives. Day 1 intensive PK will be collected in Mini Age Cohort 1 to obtain an early estimate of AUC to confirm that the appropriate dose is selected for Mini Age Cohort 2. The PK sampling at TW8 facilitates an assessment of PK exposure when ALT and/or AST elevations are anticipated to be maximal, if there are elevations.

The total blood volume required for PK analyses of both GZR and EBR (combined) is 1 mL per sample. The recommendations on safe blood sample volume limits for pediatric clinical research is provided in literature [Jack, R. 2001]. The total blood volume at each visit, accounting for PK and other sample collections is below the maximum blood limit requirements per blood draw on each visit. Also, the total blood volume collected within any 30-day period is below the maximum blood limit requirements.

Recording and Entering Meal/Soft Food Vehicle Information

- Participants will be provided an SMD which contains instructions for recording meal data that includes what they eat/drink and the time of the meal. Participants or an observer (legally acceptable representative/caregiver) should record ALL meal data from 48 hours BEFORE the PK visit through the day of the PK visit.
- Participants receiving EBR/GZR pediatric formulation should record the soft food that EBR and GZR granules were mixed into as well as the pediatric formulation food consumption timeframe (ie, the time from mixing of medication into the soft food vehicle to complete consumption of all granules that were mixed into the soft food). Participants or an observer should record this information in the SMD for all doses.
- The site will be responsible for entering the appropriate data from the SMD, as well as the qualitative fat content of the meal, in the eCRF according to the eCRF Entry Guidelines. Meal data should be entered by the site as follows:
    - For visits on Day 1 (there will be no meal data entry for pre-dose sample on Day 1), Week 4, and Week 8:
        - Enter all meal data within **2 hours before, and up to 1 hour after** the EBR/GZR dose administered on the day **prior** to the predose PK visit.
        - Enter all meal data within **2 hours before, and up to 1 hour after** the EBR/GZR dose administered at the study site.

- For participants who may take multiple meals during the time window, a separate meal entry is recorded on the eCRF for each meal within the window.
  - The soft food vehicle as well as the pediatric formulation food consumption timeframe recorded in the SMD for each dose of pediatric formulation should be entered in the eCRF.

Table 9 Pharmacokinetic Sampling Timepoints for All Age Cohorts

Study Day/Week	Time Relative to Last Dose of EBR/GZR[1, 2]
Day 1	Mini Age Cohort 1: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, 24 hr postdose All other Cohorts: Predose, 2 hr, 4 hr postdose
Week 4	All Cohorts: Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, 24 hr postdose
Week 8	All Cohorts: Predose and 2 hr postdose
HCV Viral Failure Confirmation Visit (if applicable)	All Cohorts: Anytime
Early Discontinuation Visit (if applicable)	All Cohorts: Anytime

1 mL of blood will be collected at each specified time point for plasma PK assessments of EBR/GZR (1 mL whole blood is enough for both analytes)

[1] The date and time of the last EBR/GZR dose prior to each PK sample collected must be recorded in INFORM

[2] The time of each PK sample collection relative to last dose of EBR/GZR must be recorded in INFORM

Note: At the time of PK sample collection, reference the participant's Study Medication and Meal Diary to obtain the date and time of the last dose of EBR/GZR, prior to the PK sample collection. The participant (or their caregiver, surrogate, or legally acceptable representative) should be asked to confirm the date and time are correct.

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

Leftover main study plasma from HCV RNA stored for future research.

Leftover main study plasma from viral resistance stored for future research.

9.9 Biomarkers

Biomarkers will be evaluated as part of the Future Biomedical Research sub-study.

9.10 Palatability and Acceptance Assessment

The PAA (see Appendix 7) is to be completed for all participants at the time of EBR/GZR administration at TW4 and TW8 of the study. The PAA should be implemented with the following recommendations:

- **Ages 3-4 years**: Completion by an observer (legally acceptable representative/caregiver/healthcare provider).
- **Ages 5-13 years**: Combined completion where the participant completes the faces question, and the observer completes the remaining questions.
- **Ages 14-18 years**: Completion directly by the participant, preferred when possible.

Observer assessments should be based on what the legally acceptable representative/caregiver/healthcare provider has observed directly during and after medication administration, including the participant's facial expressions, behavior, and what the participant says. Only individuals who have actually observed the participant taking the medication should complete the assessment.

9.11 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.11.1 Screening

Within 45 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6 – Study Population.

The investigator will discuss with each potential participant the nature of the study, its requirements, and its restrictions. Verification should be obtained to confirm the participant's cirrhosis status; the participant's fibrosis score must be reported to support secondary data analysis.

Screening procedures may be repeated after consultation with the Sponsor.

Rescreening

Participants who have previously completed the screening visit (Visit 1) and were deemed eligible for allocation into this study, but failed to be allocated within the 45-day window, may be rescreened to re-evaluate study eligibility. To reconfirm the participant's eligibility, all pre-study evaluations should be repeated, after approval from the Sponsor, except for the following:

- HCV GT determination
- HCV Viral Resistance/RAS

- Hepatitis B virus screening
- HIV serology
- Liver biopsy/FibroScan®
- Liver imaging
- 12-lead ECG

If any of the laboratory or ECG exclusion criteria are met, the site may have the abnormal value retested one time.

9.11.2 Treatment Period

Drug Dispense

Sites should dispense open-label containers of EBR/GZR FDC tablets (2 open-label containers at Day 1 and 1 container at each subsequent dispensing visit) or EBR and GZR pediatric formulation packets at each dispensing visit per the SoA.

An unscheduled visit must occur to get additional medication if the participant will run out of study medication prior to the next scheduled visit.

Dosing

Administration of study medication will be witnessed by the investigator and/or study staff at the first treatment visit and recorded on the participant's SMD. Participants should complete study therapy as defined by the treatment regimen and per Section 7 – Treatments. If dosing is missed or interrupted, the assigned study therapy regimen should still be completed as per Section 7.6 – Treatment Compliance. Additional instructions related to drug administration on PK visit days is provided in Section 9.6.1 – Blood Collection for Plasma EBR/GZR.

Study Medication and Meal Diary

The investigator/study coordinator will give the participant/legally acceptable representative an SMD to be completed during the treatment period of the study. The investigator/study coordinator will be responsible for entering the participant's identification (allocation number), visit number, and the dates before giving the SMD to the participant/legally acceptable representative. The participant/legally acceptable representative will be instructed to record dates/times and the number of tablets/packets of study medication dosed in the SMD for the entire treatment period as well as soft food information (participants on EBR/GZR pediatric formulation only) and meal data as described in Section 9.6.1 – Blood Collection for Plasma EBR/GZR. Only the participant/legally acceptable representative should enter information into the SMD. The participant/legally acceptable representative is to return the completed SMD at each scheduled visit. At all visits during the treatment period, site personnel must verify the accuracy of the dosing SMD by comparing entries with amounts of unused study medication. If a discrepancy is noted, investigator/ study coordinator must discuss the discrepancy with the participant/legally acceptable representative, and the explanation must be documented. Only the participant/legally acceptable representative shall make any changes to the entries on the SMD. The

investigator/study coordinator will be responsible for transferring the appropriate information from the SMD onto the appropriate case report form (CRF).

Contraception Confirmation

Throughout the treatment period precaution must be taken to avoid pregnancy in WOCBP. Confirmation must be obtained and documented by site personnel that WOCBP are using acceptable methods of contraception (see Appendix 5). This assessment must be documented in the participant's study chart at each specified visit.

9.11.3 Follow-Up Period

At the completion of study therapy, participants will be seen for follow-up visits at 4, 12, and 24 weeks after the last dose of study medication. Follow-up visits at 8, 16, and 20 weeks after the last dose of study medication will be completed by telephone contact, at which time, site personnel will confirm the participant is doing well and provide a reminder for the FW24 visit.

9.11.4 Discontinued Participants Continuing to be Monitored in the Study

Discontinuation during Treatment Period

Participants who discontinue therapy prior to the last scheduled treatment visit should complete an Early Discontinuation visit and then continue into follow-up visits.

During the Early Discontinuation visit, every effort should be made to:

- Perform all procedures and evaluations per the SoA
- Retrieve all study medication(s) from the participant
- Schedule follow-up contact(s) (telephone or site visit) as appropriate
- Collect the following information, at a minimum:
    - Reason the participant discontinued
    - Date of the last dose of study medication
    - Date of the last assessment and/or contact.
    - All AEs.

Discontinuation for Virologic Failure

Participants who discontinue because they have met criteria for virologic failure (Section 5.4.2.1.1 – HCV RNA Measurements and Endpoint Definitions) while on study therapy should complete an Early Discontinuation visit as outlined in the SoA (Section 2), and will be seen for follow-up visits at 4, 12, and 24 weeks following confirmation of virologic failure.

Participants who meet the virologic failure criterion for relapse (HCV RNA ≥LLOQ following the end of all study therapy, after becoming TND at the end of treatment) will be seen for the remainder of their follow-up visits (eg, 4, 12, and 24 weeks) as outlined in the SoA (Section 2).

Participants who have met virologic failure criteria and are identified as having a treatment-emergent RAS, will be offered follow-up in a 3-year long-term follow-up protocol, MK-5172-017, to determine the persistence of RASs and to determine time course of reversion to wild-type.

Discontinuation during Follow-up Period(s)

Participants who discontinue during the follow-up period (eg, FW4 through FW24) for reasons other than virologic failure should complete an Early Discontinuation Visit as outlined in the SoA (Section 2).

At a minimum, the following information should be collected:

- The reason the participant discontinued.
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate.
- SAEs (per reporting requirements outlined in Section 9.3 – Adverse Events, Serious Adverse Events and Other Reportable Safety.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the trial. Changes to analyses made after the protocol has been finalized will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the CSR for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

10.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan (SAP) are summarized below; the comprehensive plan is provided in Sections 10.2 to 10.12.

Study Design Overview	A Phase IIb Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Pediatric Participants Aged 3 to Less Than 18 Years with Chronic Hepatitis C Infection
Treatment Assignment	This will be an open-label, non-randomized trial. Participants infected with HCV GT1a without baseline NS5A RASs at position 28, 30, 31, and/or 93; GT1b/1-other; or GT4 with HCV RNA <800,000 IU/mL; TN or PR TE (GT1 only); cirrhotic or NC, will be treated with EBR/GZR for 12 weeks within Age Cohorts (12 to <18 years, 7 to <12 years, and 3 to <7 years). Approximately 22 participants in the oldest cohort (12 to <18 years) will be enrolled. Approximately 34 participants will be enrolled in the two younger cohorts, with 12 to 22 participants in each. The total number of participants enrolled in the three cohorts will be ~56.
Analysis Populations	PK: Per-Protocol (PP) Safety: All Participants as Treated (APaT) Efficacy: Full Analysis Set (FAS) and modified FAS (mFAS)
Primary Endpoints	$AUC_{0\text{-}24}$, C_{max}, C_{trough}, and CL/F of EBR and GZR.
Secondary Endpoints	1. Number of participants experiencing AEs and discontinuing study drug due to AEs. 2. SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy), defined as HCV RNA <LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy.
Statistical Methods for Key Pharmacokinetic and Efficacy Analyses	Geometric means and 95% confidence intervals (CIs) will be provided for $AUC_{0\text{-}24}$, C_{max}, and CL/F of EBR and GZR by age cohort and dose level. The proportion of participants achieving SVR_{12} will be estimated using a 95% CI (via the Clopper-Pearson method). The missing data approach will be Missing=Failure (M=F).
Statistical Methods for Key Safety Analyses	Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory tests. Descriptive statistics will be provided for these safety parameters.
Interim Analyses	Periodic safety analyses will be conducted for the accruing data and will be reviewed by an eDMC at regular intervals as outlined in the eDMC charter. This will supplement routine in house medical monitoring.
Multiplicity	No multiplicity adjustment is planned in this Phase IIb study.
Sample Size and Power	With 22 participants in a particular age cohort, it is ~80% likely that the lower and upper bounds of the 95% CI for EBR and GZR $AUC_{0\text{-}24}$ will lie within 44% of the observed GM.

10.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this trial will be the responsibility of the Clinical Biostatistics department of the Sponsor. The statistical analyses of the PK data will be conducted in collaboration with the Quantitative Pharmacology and Pharmacometrics and Clinical Research departments of the Sponsor.

This trial is being conducted as a non-randomized, open-label study. The Clinical Biostatistics department will generate the allocation schedule for study treatment assignment. Allocation numbers will be assigned via an IVRS/IWRS. Planned interim analyses for ongoing safety monitoring are described in Section 10.7. Study enrollment is likely to be ongoing at the time of any interim analyses. The results of interim analyses will not be shared with the investigators prior to the completion of the trial. The eDMC will serve as the primary reviewer of the results of these analyses and will make recommendations for discontinuation of the trial or protocol modifications to an executive committee of the Sponsor.

An internal statistician not otherwise connected with the trial will conduct analyses and present results to the eDMC. This statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses. Additional logistical details will be provided in the eDMC Charter. Key aspects of the interim analyses are described in Section 10.7.

10.3 Hypotheses/Estimation

There are no hypotheses to be tested in this trial. Objectives of the trial are stated in Section 4.0.

10.4 Analysis Endpoints

Pharmacokinetic, safety, and efficacy endpoints that will be evaluated are listed below.

10.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

10.4.1.1 Pharmacokinetic Endpoints

An initial description of PK endpoints is provided in Section 5.4.2.4. AUC_{0-24}, C_{max}, C_{trough}, and CL/F of EBR and GZR obtained by non-compartmental analysis (NCA) using intensive PK samples at Week 4 are the primary PK endpoints. The meal and soft food vehicle information may be considered in the PK analyses.

10.4.1.2 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 5.4.2.1. The key efficacy endpoint is SVR_{12}, (HCV RNA <LLOQ, either TD[u] or TND, 12 weeks after the end of all study therapy).

An additional efficacy endpoint is SVR_{24} (HCV RNA <LLOQ, either TD[u] or TND, 24 weeks after the end of all study therapy).

10.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 5.4.2.3 and ECIs are defined in Section 9.3.7. For this protocol, the proportion of participants who experience AEs of elevated laboratory values reported as ECIs (as described in Section 9.3.7) during the study therapy period will be estimated.

The proportions of participants with AEs of the following types at any time during the study therapy period will also be summarized: 1) with at least 1 AE; 2) with at least 1 drug-related AE; 3) with at least one SAE; 4) with at least 1 serious and drug-related AE; and 5) who discontinue due to an AE.

10.5 Analysis Populations

10.5.1 PK Analysis Population

The PP Population will serve as the primary population for the analyses of PK data in this study. The PP population consists of the subset of participants who comply with the protocol sufficiently to ensure that their PK data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment (participants' dosing compliance should be such that their PK is expected to be at steady state at the time of Week 4 assessment), availability of measurements, and absence of major protocol deviations that may affect achievement of steady state at the time of Week 4 assessment. Major protocol deviations will be identified to the extent possible prior to final database lock. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the trial, all participants who are compliant with the trial procedures as aforementioned and have available data at the Week 4 PK visit will be included in the PP population.

10.5.2 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all allocated participants who receive at least one dose of study treatment.

The mFAS will be used for supportive analysis of the efficacy endpoints of SVR_{12} and SVR_{24}. The mFAS population is a subset of the FAS population, with participants excluded for study discontinuation for reasons unrelated to the treatment regimen. Examples include loss to follow-up, discontinuation from the study due to non-drug-related AEs, informed consent withdrawal, and other non-virologic failures.

The final determination on the exclusion of participants from an analysis population will be made prior to the final database lock and will be documented in a separate memo. Details on the approach to handling missing data are provided in Section 10.6, Statistical Methods.

10.5.3 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all allocated participants who received at least one dose of study

treatment. The safety analyses will include all participants who receive any dose of active treatment, but participants who receive different doses will be reported separately.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 10.6, Statistical Methods.

10.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

10.6.1 Statistical Methods for Pharmacokinetic Analyses

Each NCA PK parameter of interest (AUC_{0-24}, C_{max}, C_{trough}, and CL/F) of EBR and GZR at Week 4 will be summarized separately by Age Cohort and treatment as appropriate, with GMs and 95% CIs based on natural log-transformed analysis and t distribution.

Individual values will also be listed for each PK parameter at Week 4 by Age Cohort and dose level as appropriate, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV) (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 × sqrt (exp(s2) - 1), where s2 is the observed variance on the natural log-scale). Descriptive statistics will also be provided for concentrations/PK parameters obtained at other time points, as appropriate.

10.6.2 Modeling and Simulation for Dose Selection

The starting dose for Mini Age Cohort 2 may be refined, if needed, based on the descriptive PK data for Day 1 from Mini Age Cohort 1. All PK data from Mini Age Cohort 1 and Mini Age Cohort 2 will be incorporated with previous adult data into the adult population PK and PBPK models, which will be continuously updated as pediatric PK data become available from each Age Cohort. Modeling and simulation will be used to select doses for Mini Age Cohort 3 and Expanded Age Cohort 1. All PK from these cohorts will in turn be used to update the models, and select the dose for Expanded Age Cohort 2/3. Dose selection by weight bands will be used. Weight bands will be determined based on PK analyses. At each step, the goal of model-based simulations will be to derive a dosing regimen expected to provide similar exposures in pediatric patients as in adults. A separate Modeling and Simulation Analysis Plan with further details on the methodology may be prepared.

10.6.3 Statistical Methods for Efficacy Analyses

Efficacy results will be presented by Age Cohorts (12 to <18 years, 7 to <12 years, 3 to <7 years). Results of participants in the Expanded Age Cohorts will be reported separately from those in the Mini Age Cohorts, unless the same dose was given to both Mini and Expanded

Cohorts within the age group. If all participants in an Age Cohort received the same dose, then results of participants in both Mini and Expanded Age Cohorts will be reported together.

Missing Values

A missing data point for a given study visit may be due to any one of the following reasons: a visit occurred but data were not collected or were unusable; a visit did not occur; or a participant discontinued from the study before reaching the visit. Participants who prematurely discontinued the assigned treatment are encouraged to remain in the study for the follow-up, if possible.

The HCV RNA outcome is categorized as TND, TD(u), and TD(q). There are 3 types of missing data handled by different approaches.

Type 1 is intermittent missing:

- Intermittent missing: If a missing data point is immediately preceded and followed by non-missing HCV RNA outcomes, the missing value will be imputed to the worst outcome of the two. For example, if a missing data point is preceded by TD(q) and followed by TD(u) or TND, then the missing value would be imputed as TD(q); if a missing data point is preceded by TD(u) and followed by TND, then the missing value would be imputed as TD(u); when a missing value is flanked by two TND, then the missing value would be imputed as TND.

Type 2 and 3 are both non-intermittent missing, but differ regarding their relationship to the study drug:

- Type 2 -- Non-intermittent missing related to the study drug: Missing values due to premature study discontinuations with reasons related to treatment either for safety or efficacy.
- Type 3 -- Non-intermittent missing unrelated to the study drug: Missing data due to premature study discontinuations with reasons unrelated to treatment such as loss to follow-up, protocol violation, withdrawal of consent/assent, administrative reasons, etc.

The following two approaches will be used to handle non-intermittent missing data (Type 2 and 3) due to premature discontinuations, depending on the analytical strategy, as described in the section below and in Table 10.

- Missing = Failure (M=F) approach: Participants with non-intermittent missing results (ie, Type 2 or Type 3 missing) will be imputed as having failed, regardless of the reason for study discontinuation.
- Treatment-Related Discontinuation = Failure (TRD=F) approach: Participants with treatment-related Type 2 missing data will be considered as having failed; whereas participants who have Type 3 missing values and have not experienced virologic failure during the observed study period will be excluded from the analysis for the time points following their study withdrawal. Participants with documented virologic failure during the treatment or follow-up period, even if they withdrew prematurely due to reasons not related to study drug, are classified as failures.

In addition, a missing baseline/Day 1 HCV RNA result will be replaced with a screening result, if available.

Proportions of Participants With Virologic Responses

For the efficacy analysis to estimate the proportion of participants achieving SVR_{12}, a 95% CI will be calculated using the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S 1934]. The missing data approach of M=F described above will be utilized for the key analysis. The same method will be used to analyze all binary endpoints.

Sensitivity analyses will be performed for the primary endpoint using the mFAS population and the TRD=F missing data approach.

Table 10 includes a summary of the key efficacy analyses.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time point)	Primary vs Secondary Approach[†]	Statistical Method	Analysis Population	Missing Data Approach[‡]
Proportion of participants achieving SVR_{12}	P	95% Confidence Interval (Clopper-Pearson)	FAS	M=F
Proportion of participants achieving SVR_{12}	S	95% Confidence Interval (Clopper-Pearson)	mFAS	TRD=F

[†] P=Primary approach; S=Secondary approach.
[‡] Imputation for specific missing values described in Section 10.6.2.
FAS = Full Analysis Set; M=F = Missing = Failure; mFAS = modified Full Analysis Set; TRD=F = Treatment-Related Discontinuation = Failure.

Participant Virologic Failure: Non-Response, Rebound, Breakthrough, or Relapse

Summary statistics will be provided to describe the rates of occurrence of virologic non-response, rebound, breakthrough, or relapse. Definitions for virologic non-response, rebound, breakthrough, or relapse are in Section 5.4.2.1.1.

10.6.4 Statistical Methods for Safety Analyses

Safety results will be presented by Age Cohorts (12 to <18 years, 7 to <12 years, 3 to <7 years). Results of participants in the Expanded Cohorts will be reported separately from those in the Mini Cohorts, unless the same dose was given to both Mini and Expanded Cohorts within the age group.

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs and laboratory parameters.

The analysis of safety parameters will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed.

The first tier includes (1) AEs of elevated laboratory values that are reported as ECIs described in Section 9.3.7; (2) any AE; (2) a drug-related AE; (4) an SAE; (5) a serious and drug-related AE; and (6) an AE leading to discontinuation. Point estimates and 95% CIs will be provided for the proportion of participants with first tier AEs. The 95% CIs for the safety parameters will be estimated using the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S 1934].

The second tier includes specific AEs by system organ class, vital signs, and standard laboratory safety tests at time points specified in the SoA. Point estimates will be provided for the proportion of participants with second tier AEs.

Missing safety laboratory or vital signs will be handled using the Data As Observed approach, that is, any missing value will be excluded from the analysis. The only exception is when a Baseline/Day 1 result is missing, this will be replaced with the latest pre-treatment result, if available.

The primary safety analysis will summarize the safety data for participants during the treatment period plus 14 days of follow-up.

Table 11 Analysis Strategy for Safety Parameters

Safety Endpoint	95% CI	Descriptive Statistics
AEs of elevated laboratory values that are reported as ECIs	X	X
Any AE	X	X
Any Serious AE	X	X
Any Drug-Related AE	X	X
Any Serious and Drug-Related AE	X	X
Discontinuation due to AE	X	X
Specific AEs or SOCs or PDLCs		X
Change from Baseline Results (laboratory vital signs)		X
95% confidence intervals will be calculated using the Clopper-Pearson method. Note: AE = adverse event; CI = confidence interval; ECI = event of clinical interest; PDLC = pre-defined limits of change; SOC = System Organ Class; X = results will be posted.		

10.6.5 Summaries of Baseline Characteristics, Demographics, and Other Analyses

10.6.5.1 Demographic and Baseline Characteristics

Baseline characteristics for all allocated and treated participants will be summarized by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and allocated, and the primary reasons for screen failure and discontinuation will be displayed. Demographic variables (eg, age, gender, race, and GT subtype) and prior and concomitant therapies will be summarized using descriptive statistics for continuous or categorical variables, as

appropriate. Summary statistics for baseline efficacy measures such as HCV RNA will also be provided.

10.6.5.2 Growth

Height and weight will be compared to the normative population based on age as well as the mid-parental height. Summary statistics and changes from baseline at each time point during follow-up will be reported, where baseline is the start of the treatment period.

10.6.5.3 Viral Resistance Measurements

Viral resistance testing will focus on the entire NS3/4A and NS5A regions for all participants and for those who meet the virologic failure criteria (see Section 5.4.2.1.1).

10.6.5.4 Palatability and Acceptance Assessment

Each participant will rate the palatability and respond to questions on the acceptability of treatment with EBR/GZR on TW4 and TW8 of the study. This will be based on the FHS facial expression scale depicting various degrees of pleasure as an assessment of palatability (Section 5.4.2.2 and Section 9.10).

Descriptive statistics will be used to summarize the palatability and acceptability responses. Missing data will not be imputed, and the analyses will be based on observed data only. These analyses will be based on the FAS population.

10.7 Interim Analyses

To supplement the routine safety monitoring outlined in this protocol, the eDMC will monitor ongoing safety data and provide recommendations to ensure the safety of study participants and the integrity of the trial to the EOC (see Appendix 3 – Committees Structure – Executive Oversight Committee). HCV RNA data may be included as part of the reviews to allow for an assessment of benefit-risk. The eDMC will monitor the trial with suggested periodic reviews to occur approximately every 6 months. An internal statistician not otherwise connected with the trial will conduct the analyses and present results to the eDMC.

10.8 Multiplicity

There will be no multiplicity adjustments in the analysis of this trial.

10.9 Sample Size and Power Calculations

10.9.1 Sample Size and Power for PK Analyses

The precision of the estimates of EBR and GZR PK obtained from this study can be described in terms of the relative length of the 95% CIs expected for the given sample size and assumed variability. The calculations for AUC_{0-24} below are based on assumed true between-subject standard deviations (log-scale) of 0.452 and 0.731 for EBR and GZR, respectively, as observed in MK-5172 Protocol 059 (a Phase II/III non-randomized, unblinded, open-label study that evaluated the efficacy and safety of EBR/GZR in subjects with chronic HCV and advanced cirrhosis and hepatic insufficiency) and take into account

the sampling distribution of the observed sample variance as described in Wang et al [Wang, Y., et al 2012].

For the given sample size and assumed between-subject variability, there is ~80% probability that the 95% CI for the true GM AUC_{0-24} will lie within the ranges shown in Table 12, expressed relative to the observed GM. For example, given 22 participants in an Age Cohort, it is ~80% likely that the lower and upper bounds of the 95% CI for GZR AUC_{0-24} will lie within 44% of the observed GM.

Table 12 Expected Precision (80% Likely) for Estimates of GZR and EBR AUC_{0-24}

Analyte	N	95% CI within *X* % of Observed GM
GZR	5	± 204%
	12	± 71%
	15	± 59%
	22	± 44%
EBR	5	± 99%
	12	± 40%
	15	± 33%
	22	± 25%

10.9.2 Sample Size and Power for Efficacy Analyses

The key efficacy objective will be assessed based on the proportion of participants achieving SVR_{12}, defined as HCV RNA <LLOQ 12 weeks after the end of all study therapy. This is an estimation study with no hypotheses. The expected response rate is ~95% based on previous EBR/GZR clinical trials. Treatment is expected to be similarly active in different Age Cohorts in either TN or TE pediatric participants with or without cirrhosis.

Efficacy results will be presented by Age Cohorts. Results of participants in the Expanded Cohorts will be reported separately from those in the Mini Cohorts, unless the same dose was given to both Mini and Expanded Cohorts within the age group. If all participants in an Age Cohort receive the same dose, then results of participants in Mini and Expanded Cohorts will be reported together. Table 13 shows the 95% CIs for SVR_{12} given varying assumptions of number of successes for 5, 12, 15, and 22 participants. Note that the intervals are not symmetric around the point estimate.

Table 13 Two-Sided 95% Confidence Intervals for SVR_{12} (FAS Population)

	Observed Number of Successes (%)	Two-Sided 95% Confidence Interval†
N=5	3 (60.0%)	(14.7, 94.7)
	4 (80.0%)	(28.4, 99.5)
	5 (100.0%)	(47.8, 100.0)
N=12	9 (75.0%)	(42.8, 94.5)
	10 (83.3%)	(51.6, 97.9)
	11 (91.7%)	(61.5, 99.8)
	12 (100.0%)	(73.5, 100.0)
N=15	12 (80.0%)	(51.9, 95.7)
	13 (86.7%)	(59.5, 98.3)
	14 (93.3%)	(68.1, 99.8)
	15 (100.0%)	(78.2, 100.0)
N=22	18 (81.8%)	(59.7, 94.8)
	19 (86.4%)	(65.1, 97.1)
	20 (90.9%)	(70.8, 98.9)
	21 (95.5%)	(77.2, 99.9)
	22 (100.0%)	(84.6, 100.0)

FAS = Full Analysis Set
† Based on the two-tailed exact confidence interval for a binomial proportion (Clopper and Pearson) [Clopper, C. J. and Pearson, E. S 1934]

10.9.3 Sample Size and Power for Safety Analyses

The key safety objective of this study will be assessed by a review of the accumulated safety data. Certain safety endpoints of special interest have been identified in Section 10.6.3 of this document. Safety results will be presented by Age Cohorts. Results of participants in the Expanded Cohorts will be reported separately from those in the Mini Cohorts, unless the same dose was given to both Mini and Expanded Cohorts within the age group. If all participants in an Age Cohort received the same dose, then results of participants in Mini and Expanded Cohorts will be reported together.

The probability of observing at least one of a particular type of AE depends on the number of participants treated and the underlying percentage of participants with that AE in the study population. For instance, if the underlying incidence of a particular AE is 1% (1 of every 100 participants receiving the drug), there is a 20% chance of observing at least one AE of that type among 22 participants. If no AE of that type is observed among the 22 participants, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <15.4%.

The estimate of, and the upper bound of the 95% CI for, the underlying percentage of participants with an AE given various hypothetical observed number of participants with the AE are provided in Table 14. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S 1934].

Table 14 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs

N	Hypothetical Number of Participants with an AE (Estimate of Incidence)	95% Upper Confidence Bound†
5	0 (0.0%)	52.2%
	1 (20.0%)	71.6%
12	0 (0.0%)	26.5%
	1 (8.3%)	38.5%
	2 (16.7%)	48.4%
15	0 (0.0%)	21.8%
	1 (6.7%)	31.9%
	2 (13.3%)	40.5%
	3 (20.0%)	48.1%
22	0 (0.0%)	15.4%
	1 (4.5%)	22.8%
	2 (9.1%)	29.2%
	3 (13.6%)	34.9%
	5 (22.7%)	45.4%

†Based on the two-tailed exact confidence interval for a binomial proportion (Clopper and Pearson) [Clopper, C. J. and Pearson, E. S 1934].

10.10 Subgroup Analyses

To assess the consistency of the response across various subgroups, the SVR_{12} rate and associated 95% CIs will be estimated within each category of the following classification variables:

- Sex (female, male)
- GT (1a, 1 non-a, 4)
- Age (3 to <7 years, 7 to <12 years, 12 to <18 years)
- HCV RNA at baseline, (≤800,000 IU/mL, >800,000 IU/mL; ≤2 million IU/mL, >2 million IU/mL)
- Stage of fibrosis (Non-cirrhotic, Cirrhotic)
- Prior treatment history (TN, TE)
- Weight bands

The analyses by weight bands may be performed separately by age cohort and/or separately for Mini and Expanded Age Cohorts.

10.11 Compliance (Medication Adherence)

In this trial, the SMD will be used to monitor and document a participant's drug compliance. Data reported on the SMD will serve as the primary data for compliance analysis.

A day within the study will be considered an "On-Therapy" day if the participant takes the assigned treatment as noted in Section 7.5.1.

For a participant who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from dosing to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from dosing to the date of the last dose of study medication.

For each participant, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100$$

Summary statistics will be provided for percent compliance for the FAS population.

10.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary statistics (N, mean, and range) for the "Number of Days on Therapy".

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Term	Definition
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
APaT	All Participants as Treated
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
AUC_{0-24}	AUC over 24 hours
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum observed drug concentration
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical Study Report
C_{trough}	Plasma concentration immediately predose
CYP3A	Cytochrome P450 3A
CV	Coefficient of variation
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EBR	Elbasvir
ECG	Electrocardiogram
ECI	Events of clinical interest
eDMC	External Data Monitoring Committee
EOC	Executive Oversight Committee
ERC	Ethics Review Committee
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration, US
FDC	Fixed dose combination
FHS	Facial hedonic scale
FW	Follow-up Week
GM	Geometric mean
GT	Genotype
GZR	Grazoprevir
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV-1	Human immunodeficiency virus type 1
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Institutional Ethics Committee
IFN	Interferon
INR	International normalized ratio
IRB	Institutional Review Board
IVRS/IWRS	Interactive voice response system/integrated web response system
LLOQ	Lower limit of quantification
M=F	Missing = Failure
mFAS	Modified Full Analysis Set
NCA	Non-compartmental analysis
OATP	Organic anion-transporting polypeptide

Term	Definition
PAA	Palatability Acceptance Assessment
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PP	Per-Protocol
PR	Pegylated-interferon with RBV
QD	Once daily
RAS	Resistance-associated substitution
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sSAP	Supplemental Statistical Analysis Plan
SMD	Study Medication and Meal Diary
SoA	Schedule of Activities
SVR	Sustained virologic response
SVR_{12}	Sustained virologic response 12 weeks after the end of all study therapy
SVR_{24}	Sustained virologic response 24 weeks after the end of all study therapy
TD(q)	Target detected, quantifiable
TD(u)	Target detected, but unquantifiable
TE	Treatment-experienced
TK	Toxicokinetic
T_{max}	Time to maximum concentration
TN	Treatment-naïve
TND	Target not detected
TRD=F	Treatment-Related Discontinuation = Failure
TW	Treatment Week
ULN	Upper limit of normal
US	United States
WOCBP	Woman of childbearing potential

12.2 Appendix 2: Clinical Laboratory Tests

- Laboratory tests to be performed in this study are specified in Table 15 and will be conducted by the central laboratory. The total amount of blood/tissue to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in Table 16.

Table 15 Protocol-Required Safety Laboratory Assessments

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	**Coagulation Panel** –PT –INR
Hemoglobin	ALP	Glucose	Choriogonadotropin beta (urine pregnancy test kits to sites)
Platelet count	ALT	Protein	Serum human chorionic gonadotropin (reflex when urine pregnancy test is "positive")
RBC	AST	Specific gravity	HCV, Genotype
WBC	Bicarbonate	Microscopic exam (if abnormal results are noted)	HCV, Viral Load RNA (quantitative)
WBC Differential (result in % and Abs) –Basophils –Eosinophils –Lymphocytes –Monocytes –Neutrophils (Total)	Calcium	Bilirubin	FibroScan®
	Chloride	Ketones	
	Creatinine	Leukocyte esterase	**Hepatitis B Serology Panel** –HBsAg (perform at screening in all participants
			–Anti-HBc, Total (screening only)
	Creatinine clearance (eGFR estimated by MDRD–NKDEP) (screening only)	Nitrite	**HIV Serology Panel** –HIV, Types 1 & 2 –HIV, Types 1 & 2 Confirmation by Inno-Lia HIV score–
	CPK	pH	(

Hematology	Chemistry	Urinalysis	Other
	GGT	WBC	
	Amylase	Bacteria	
	Lipase	Squamous epithelial cells	
	Glucose	RBC	
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin (if total bilirubin is elevated above the ULN)		
	Total protein		
	Blood urea nitrogen		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; Anti-HBc=hepatitis B core antibody; Anti-HBs=hepatitis B surface antibody; AST=aspartate aminotransferase; CPK=creatine phosphokinase; eGRF=estimated glomerular filtration rate; GGT=gamma-glutamyl transpeptidase; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; MDRD-NKDEP=Modification of Diet in Renal Disease–National Kidney Disease Education Program; PT=prothrombin time; RBC=red blood cell; RNA=ribonucleic acid; ULN=upper limit of normal; WBC=white blood cell.

Abbreviated blood chemistry includes only ALT, AST, ALP, total bilirubin, albumin, GGT, and CPK

Table 16 Approximate Blood Volumes Collected

Test	Screening	Day 1	TW 2	TW 4	TW 6	TW 8	TW 10	TW 12	FW 4	FW 12	FW 24	Total Volume in mL
Coagulation	1.8	1.8				1.8		1.8		1.8	1.8	10.8
HBsAg Anti-HBc	2											2
Chemistry (complete)	2	2		2		2		2		2	2	14
Chemistry (abbreviated)			2		2		2		2			8
Hematology	2	2		2		2		2	2	2	2	16
EBR/GZR PK		3[1]		10		3						16[2]
HCV Genotype	4											4
HCV RNA Level	4			4		4		4	4	4	4	28
HCV Viral Resistance/ Resistance Associated Substitutions (RAS)	4								4	4	4	16
HIV Serology	4											4
Total Volume in mL	23.8	8.8[3]	2	18	2	12.8	2	9.8	12	13.8	13.8	118.8[4]

[1] Subjects in Mini Age Cohort 1 only (age 12 to <18 years; N=7) will have 10 mL of blood drawn for PK sampling on Day 1. All other participants will have 3 mL of blood drawn for PK sampling on Day 1.
[2] Subjects in Mini Age Cohort 1 only (age 12 to <18 years; N=7) will have a total of 23 mL of blood drawn for PK sampling. All other participants will have a total of 16 mL of blood drawn for PK sampling.
[3] Subjects in Mini Age Cohort 1 only (age 12 to <18 years; N=7) will have a total of 15.8 mL of blood drawn on Day 1. All other participants will have a total of 8.8 mL of blood drawn on Day 1.
[4] Subjects in Mini Age Cohort 1 only (age 12 to <18 years; N=7) will have a total of 125.8 mL of blood drawn overall. All other participants will have a total of 118.8 mL of blood drawn overall.

12.3 Appendix 3: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research participant by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for participant referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying

worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

Committees Structure

Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the trial.

Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

Publication Policy

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are participant to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." • Any new cancer or progression of existing cancer.

Events NOT Meeting the AE Definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to section 9.3.5 for protocol specific exceptions

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE
● In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes. ● Is a new cancer; ● Is associated with an overdose.

Recording AE and SAE

AE and SAE Recording
● When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. ● The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination. ● It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page. ● There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. ● The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric trials, awareness of symptoms, but easily tolerated)
  - Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric trials, definitely acting like something is wrong)
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric trials, extremely distressed or unable to do usual activities).

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by

another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in consistently and correctly during the protocol-defined time frame in Section 6.1.

Table 17 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment . c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment additional pregnancy testing will be performed every 4 weeks during the treatment period and at 4 weeks, after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

12.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Sample Collection will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the participants on the visit designated in

the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the participant is having blood drawn for other trial purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (ie, only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.7 Appendix 7: Palatability and Acceptance Assessment Form

THE COMBINATION REGIMEN OF GRAZOPREVIR (GZR)/ELBASVIR (EBR) +/- RIBAVIRIN (RBV) IN PEDIATRIC SUBJECTS WITH CHRONIC HEPATITIS C INFECTION

PAA

Compound	Protocol	Visit
MK-5172	079	

Screening No. *(Site - Sequence No.)*	Randomization No.
_ _ _ _ _ - _ _ _ _ _ _	_ _ _ _ _ _ _

PALATABILITY AND ACCEPTANCE ASSESSMENT (PAA)

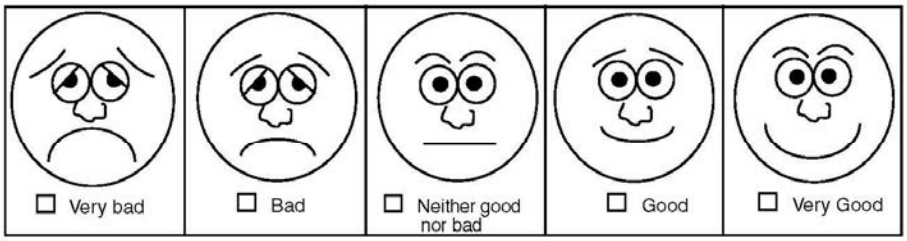
Specify completion date: _____
DD-Mon-YYYY

Please mark one box below to identify the person entering the responses on the questionnaire.

- ☐ The patient
- ☐ The patient/primary caregiver
- ☐ The patient and parent/primary caregiver
- ☐ The health care provider (e.g., physician, nurse, medical assistant or nursing assistant caring for the patient)

This form should be completed at the time of oral medication administration.
Please answer all questions.

1. Please mark the box of one picture below to show how you/the patient feels about the taste of the medication:



☐ Very bad ☐ Bad ☐ Neither good nor bad ☐ Good ☐ Very Good

2. Please indicate if you/the patient had any of the following problems when taking the medication by mouth:

a. Refusing	☐ Yes	☐ No
b. Spitting Out	☐ Yes	☐ No
c. Throwing Up or Spitting Up	☐ Yes	☐ No
d. Gagging	☐ Yes	☐ No
e. Other, specify	☐ Yes	☐ No _____

3. Are there any other comments related to the taste of the medication? ☐ Yes ☐ No

Specify comments: _____

_____

_____

I confirm this information is accurate.	Subject's/Caregiver's Initials:	Date:

I have reviewed this information.	Staff Initials:	Date:

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