Official Protocol Title:	A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been Previously Treated with MK-5172 in a Prior Clinical Trial
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TITLE:

A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been Previously Treated with MK-5172 in a Prior Clinical Trial

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: III

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SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
All	All	The protocol has been updated to include enrollment of pediatric subjects from protocol MK-5172 PN079. Where applicable, sections, enrollment criteria, and/or procedures for the pediatric population have been added. In addition, enrollment criteria and/or procedures specific to the adult population have been clarified.	Subjects enrolled in the pediatric protocol MK-5172 PN079 who experience virologic failure associated with one or more treatment-emergent resistant associated substitutions (RASs) can enroll in this study. Clarification between the adult and pediatric populations has been added to ease review of the protocol by investigators.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.1.1.1	Adult Population (subsection of Primary Objectives and Hypotheses)	**Primary Objective #1:** • **Original wording**: To evaluate the durability of SVR in subjects who remained HCV RNA < LLoQ (either TND or TDu) throughout the follow-up period of the treatment protocol and did not start any new HCV therapy between the end of the previous protocol and entry in this study. o All subjects (except subjects from PN 052) with HCV RNA < LLoQ will be discontinued from PN 017 after the next scheduled visit. PN 052 subjects will remain for a duration of 5 years as introduced in AM02. Data collected up to a subject's last visit will be assessed for durability. After AM03 approval, no additional subjects achieving SVR will enroll in PN 017. • **Amendment 04 wording**: To evaluate the durability of response in subjects who achieved SVR_{24} in the prior treatment study and at the time of entry into PN017 were HCV ribonucleic acid (RNA) <lower limit of quantification (LLoQ) (either target not detected [TND] or target detected, unquantifiable [TD(u)]).	The previous wording ("throughout the follow-up period…") was too rigid and excluded subjects who had a transient HCV RNA increase. Sub-bullet text was deleted because it is found in other sections of the protocol.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.1.1.1	Adult Population (subsection of Primary Objectives and Hypotheses)	**Primary Objective #2:** • **Original wording:** To evaluate the presence of antiviral resistance, NS3/4A, NS5A and/or NS5B, (as appropriate) and determine if there is a reversion to a wild-type pattern within the 3 years (all protocols except PN 052) or 5 years timeframe for PN 052 of this long-term follow-up study. o Subjects enrolling in PN 017 with quantifiable HCV RNA after having failed therapy will be followed for 3 years (all studies except PN 052) or 5 years (PN 052) • **Amendment 04 wording:** To evaluate the presence of treatment-emergent antiviral resistance to NS3/4A, NS5A and/or NS5B regions, (as applicable) and determine if there is a reversion to wild-type pattern within the 3-year time frame of this long-term follow-up study (or 5-year time frame for subjects from PN052) in subjects with virologic failure in the prior treatment study and with HCV RNA ≥1000 IU/mL in Protocol 017.	The new wording of this objective reflects the current interest in the focus on treatment-emergent RASs and the persistence of these RASs. Additionally, wording was added to align with Merck's standard methodology for resistance testing (ie, resistance can only be assessed in subjects when HCV RNA levels are >1000 IU/mL). Sub-bullet text was deleted because it is found in other sections of the protocol.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.2	Subject Inclusion Criteria	**Inclusion #3:** • **Original wording:** Subject must be ≥ 18 years of age and willing to give written informed consent. • **Amendment 04 wording:** Subject is male or female 3 years of age or older on day of signing informed consent/assent. **Inclusion #4:** • **Original wording:** Subjects who have consented for the trial may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research. • **Amendment 04 wording:** Subject or subject's legally acceptable representative provides written informed consent (or written informed assent where applicable). Subjects who have consented for the study may also provide consent/assent for Future Biomedical Research (FBR). However, the subject may participate in PN017 without consenting/assenting for FBR.	Revised inclusion criterion #3 and #4 and added inclusion criterion #6 to allow for enrollment of subjects to this study from the pediatric protocol MK-5172 PN079.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		Inclusion #6: **Amendment 04 added:** Pediatric subject must have received at least 1 dose of a GZR-containing regimen and experienced virologic failure with 1 or more associated treatment-emergent RASs at FW12 in PN079.	
2.3	Exclusion Criteria	**Exclusion #1:** • **Original wording:** In the opinion of the investigator, if a subject is mentally or legally incapacitated at entry, the subject may be excluded. • **Amendment 04 wording:** **Adult subjects**: In the opinion of the investigator, subject is mentally or legally incapacitated at entry into PN017. **Pediatric subjects**: The subject has significant emotional problems or a clinically significant psychiatric disorder that may interfere with participant treatment, assessment, or compliance with the protocol.	The criterion was updated to be specific to adults and pediatric subjects.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.7.1.1	Adult Population (subsection of Efficacy Analyses)	Aligned the description of the primary objective, to state "the primary efficacy objectives of this study are to evaluate the durability of response in subjects who achieved SVR in the prior treatment study..."	This change was made to streamline the presentation of information and align with changes made to Section 2.1.1.1.
6.2.1 and 6.2.2	Adult Blood Volumes and Pediatric Blood Volumes	Tables added in each subsection.	Blood volumes defined per visit for adult and pediatric subjects.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
All sections	All sections	1. Changed MK-5172 to grazoprevir (GZR), MK-8742 to elbasvir (EBR), MK-8408 to ruzasvir (RZR), and MK-3682 to uprifosbuvir (UPR).	1. Updated to include approved generic names.
		2. Changed the word "trial" to "study."	2. Updated the protocol to use "study" consistently throughout the document.
		3. Changed adverse experiences to adverse events.	3. Updated the protocol to be in alignment with standard nomenclature.
		4. Changed "patients" to "subjects".	4. The term "subjects" is used throughout for consistency.
		5. The term "resistance associated variant" (RAV) was replaced with "resistance associated substitution" (RAS).	5. "Resistance associated substitution" has recently been adopted as the preferred nomenclature [1]. It should be noted that in earlier documents, including the original study protocol, the term RAV was used to describe RAS.
		6. Other editorial and document formatting revisions.	6. Minor, and therefore have not been summarized.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1	Summary	All subsections within the Summary were revised to provide updated information and streamline the text.	Revised to align with standard for Merck-authored HCV protocols.
1.7.1	Study Flow Chart, Adult Population	Deleted description of medical history procedures; condensed Child-Pugh score compilation to one line; added Visits 8 and 10 to review of ECIs and AEs; and clarified visit window duration.	These changes were made to correct inconsistencies, provide concise display, and to improve clarity of the protocol.

2.3	Subject Exclusion Criteria	**Exclusion #3:**
		• **Original wording:** For Amendment 03: Subjects who fail therapy due to re-infection are excluded.
		• **Amendment 04 wording**: Starting with AM 03: Subjects who failed therapy due to re-infection, defined as:
		  • an HCV RNA sample with a different genotype than the baseline genotype in the prior treatment study, or
		  • an HCV RNA sample determined to be reinfection by phylogenetic analysis with comparison to the baseline sequence in the prior treatment study.
			The definition of subjects who failed therapy was added to exclusion criterion #3 to improve clarity of the protocol.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.4.1.1	Adult Population (subsection of Summary of Study Design)	Item #2: • **Original wording:** Subjects in PN 017 who entered with quantifiable HCV RNA will continue for 3 years of follow-up (except PN 052 subjects) or 5 years of follow-up (PN 052). • **Amendment 04 wording:** Subjects in PN017 with virologic failure at FW24 in the prior treatment study will continue for 3 years of follow-up (other than PN052 subjects) or 5 years of follow-up (PN052 subjects).	Item #2 was revised because virologic failure criteria is based on failing in the prior treatment study.
2.7	Statistical Analysis Plan Summary	Removed details from introductory statement and added reference to Section 3.5.	These changes were made to streamline the presentation of information.
3.2.1	Subject Population	Removed descriptive wording found in other sections of protocol.	These changes were made to streamline the presentation of information.
3.2.2.1	Adult Population (subsection of Concomitant Medication(s)/ Treatment(s)	Stated clearly that starting with AM 03, subjects are not permitted to take any therapies used for the treatment of HCV concurrently with this protocol.	These changes align with the changes made during AM 03 and were made to streamline the presentation of information.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.2.4	Procedures	Clarified visit window as must be performed within +/- 3 months	This change was made because all study visits are to occur every 6 months, therefore the statement, "or +/- 6 months of the scheduled visit if a year apart", is not applicable.
3.2.4.1	Screening/Baseline Visit (Visit 1)	For adult subjects, made the following revision: .."the following medical history terms, which occurred after the prior treatment study and before study entry, will be collected:"	These changes were made to improve clarity of the protocol and align collection of medical history (MH) events and events of clinical interest (ECI), as these MH and ECI events will be included for analysis.
3.2.4.8.1	Discontinuation/Withdrawal Criteria	Adjusted introductory paragraph.	These changes were made to streamline the presentation of information.
3.3.1.1	Adult Population (subsection of Clinical and Laboratory Measurements for Durability, Viral Resistance, and Safety)	Reordered details to follow the same order as the study flow chart. Updated formatting	These changes were made to streamline the presentation of information.
3.4.3.1	Serious Adverse Events	Changed title from Serious Adverse Experiences to Serious Adverse Events; Moved note regarding drug-related serious adverse event reporting.	These changes were made to provide a consistent term throughout document and highlight reporting requirements so that they are easily identified and understood by site(s).

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.4.3.2 and 3.4.3.2.1	Events of Clinical Interest and subsection for Adult Population	1. The title of Section 3.4.3.2 was changed from "Selected Adverse Experiences (if applicable)" to "Events of Clinical Interest". 2. Details were added for ECIs of hepatocellular carcinoma: **Original wording:** • Hepatocellular carcinoma **Amendment 04 wording:** • Hepatocellular carcinoma; Any hepatocellular carcinoma that occurred and was not previously reported in the prior treatment study should be reported as an ECI. 3. Details were added to define criteria for decreased eGFR for PN052 subjects: **Original wording:** • eGFR (will be analyzed for change from baseline) **Amendment 04 wording:** • Decreased eGFR calculated by the Modification of Diet in Renal Disease equation (PN052 subjects will be analyzed for change from baseline in PN052);	1. Changed to provide a consistent term of ECI throughout the document. 2. HCC: Additional wording was added to clarify the need for reporting events that occurred between the last visit of the prior treatment study and the first visit of PN017 as ECIs. Decreased eGFR: Additional wording was added to clarify when to report this as an ECI for CKD subjects. The new wording addresses the natural fluctuation in eGFR in CKD subjects.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		○ For this study a decrease in eGFR is defined for subjects not on dialysis as: ▪ CKD4 (15 to 30 ml/min/1.73 m^2) in PN052 and is now CKD5 (<15 ml/min/1.73 m^2), ▪ CKD5 without dialysis in PN 052 and is now CKD5 with dialysis, OR ▪ CKD4 in PN 052 and initiates dialysis 4. Clarified that kidney transplant, decreased eGFR, new onset diabetes, and post transplantation glomerulonephritis are ECIs recorded only for subjects who participated in PN052 as their prior treatment study.	

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.5	Statistical Analysis Plan	Deleted wording for notable changes for AM 03: **Wording removed:** With AM 03, the notable changes and/or additions to the SAP include: 1. The analysis population to characterize durability of response was refined. Specifically, the requirement that subjects needed to be TND at the end of treatment in the previous protocol in order to be included in the analysis population was removed. The analysis population for the time to relapse analysis will be all subjects who were < LLoQ during the follow-up period of the previous trial (never confirmed to be >LLoQ) and entered PN 017 with HCV RNA <LLoQ and did not start any new HCV therapy between the end of the previous protocol and entry in this study. 2. Descriptive statistics will be provided for the rate that patients with CKD (Protocol 052) require liver transplants (See Section 3.5.5.2).	The wording in #1 no longer aligns with the new objective language, therefore it was removed. The wording in #2 and #3 was included elsewhere in Section 3.5.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		3. For the analysis of viral resistance, subgroup analyses will be performed by class of regimen (e.g. NS3/4A inhibitors, NS5A inhibitors and NS5B inhibitors) as well as by specific components. (See Section 3.5.5.3)	
6.3	List of Abbreviations	Abbreviation list added.	List added as a reference for abbreviations used in the protocol.

1. SUMMARY

1.1 TITLE

A Long-Term Follow-up Study to Evaluate the Durability of Virologic Response and/or Viral Resistance Patterns of Subjects With Chronic Hepatitis C Who Have Been Previously Treated with MK-5172 in a Prior Clinical Trial

1.2 INDICATION

Grazoprevir (GZR) is being developed for treatment of chronic hepatitis C virus (HCV) infection.

1.3 SUMMARY OF RATIONALE

The HCV clinical development program has evaluated GZR in combination with pegylated-interferon, ribavirin, and other direct-acting antiviral (DAA) therapies, including elbasvir (EBR), ruzasvir (RZR), and uprifosbuvir (UPR) as various investigational HCV treatment regimens. Refer to the respective Investigator Brochures (IBs) for background information and study results for the various GZR-containing regimens.

Across the program, over 4,500 HCV-infected subjects will have received at least 1 dose of GZR in more than 20 Phase 2 and Phase 3 Merck-sponsored clinical studies (hereafter referred to as prior treatment study). The totality of Phase 2 and Phase 3 data was used to identify a highly effective combination of DAAs for the treatment of chronic HCV. During the course of development, different regimens, treatment durations, and genotypes (GTs) were assessed. Ultimately, these data were used to support the approval of the combination regimen EBR/GZR for 12 to 16 weeks in GT1 and GT4.

This study (Protocol 017; PN017) will assess: 1) durability of virologic response, 2) monitor persistence of virologic resistance, and 3) safety, including progression of liver disease, and for subjects with chronic kidney disease (CKD) from PN052, progression of kidney disease.

Enrollment in PN017 includes an adult population (aged ≥18 years) and a pediatric population (aged 3 to <18 years), based on subject age at the time of screening in the prior treatment study. While many studies are grouped together for objectives and analyses, two studies (PN052 and PN079) enrolled special populations that will be assessed apart from other populations. Subjects from PN052 all have advanced CKD (Stages 4 or 5); these subjects are followed for 5 years to understand the natural history of CKD and liver disease progression following HCV therapy. Subjects from PN079 are pediatric subjects who will be followed only if the subject experiences virologic failure with 1 or more treatment emergent RASs.

A list of abbreviations used within this protocol is in Appendix 6.3.

1.3.1 Durability of Virologic Response

At the time of PN017 initiation, FDA guidance for industry specified that HCV-infected patients treated with a DAA and achieving sustained viral response (SVR) be followed for at least 3 years to ensure durability of response. As the field of HCV therapies advanced, data accrued demonstrated that SVR observed at 12 and 24 weeks after DAA treatment was durable for years [2][3]. These findings resulted in modifications to the regulatory guidance to no longer assess durability of response beyond 24 weeks of follow-up [4]. Subjects who achieved SVR in a prior treatment study and were enrolled into PN017 were subsequently discontinued at their next visit due to amendment (AM) 03. All subjects up to discontinuation or study completion will be included in data analyses of durability of response.

1.3.2 Persistence of Virologic Resistance

Following treatment with an appropriate DAA regimen, the majority of HCV-infected subjects (>95%) achieve SVR. For subjects who do not achieve SVR, treatment failure is often accompanied by the presence or emergence of genetic mutations (resistance-associated substitutions [RAS]) that generate functional viral proteins with reduced DAA susceptibility compared to wild-type virus [5]. The presence or development of RAS may have an important impact on efficacy outcomes and retreatment options, and hence, is a concern for DAA treatment of HCV-infected adult and pediatric populations.

Thus, adult and pediatric subjects enrolled in PN017 will be followed for up to 3 years (or up to 5 years for PN052 subjects) to assess persistence of virologic resistance.

1.3.3 Safety

The natural history of liver disease after treatment with novel all-oral regimens, as well as the natural history of kidney disease of HCV-infected subjects with the co-morbidity of CKD, remains to be defined. As such, progression of liver disease and chronic kidney disease, as well as the incidence of certain cardiac and neurologic events, will be assessed.

1.3.3.1 Progression of Liver Disease (All Adult Subjects)

Progression of liver disease is assessed in all adult subjects in PN017. Specific liver related safety events are reported as events of clinical interest (ECIs) in all adult subjects; these events include: hepatocellular carcinoma, variceal bleeding, ascites, encephalopathy, liver transplant, spontaneous bacterial peritonitis, and hepatorenal syndrome.

1.3.3.2 Progression of Chronic Kidney Disease

CKD affects approximately 10% of the United States population [6] and is associated with multiple co-morbidities (eg. diabetes, hypertension, and cardiovascular disease). Thus, enrolling adult HCV-infected subjects with CKD (Stage 4 or 5, including subjects on dialysis) from the prior treatment study PN052 into PN017 offers an important opportunity to collect long-term data for this subpopulation. For HCV-infected adult

subjects with the co-morbidity of CKD, protocol-specified kidney related ECIs are collected, including change from baseline in estimated glomerular filtration rate (eGFR), new onset diabetes, cryoglobulinemia, kidney graft rejection, post-transplantation glomerulonephritis, and kidney transplant.

1.3.3.3 Other (Cardiac and Neurologic)

Cardiovascular disease and neurologic disorders limited to transient ischemic attack or stroke will be collected as ECIs for all adult subjects. These are adverse events associated with both liver and kidney disease; as such, cardiovascular disease (angina and myocardial infarction), transient ischemic attack, and stroke will be evaluated in all adult subjects.

1.4 SUMMARY OF STUDY DESIGN

PN017 is a multicenter, long-term follow-up study for HCV-infected adult and pediatric subjects previously treated with at least 1 dose of GZR in a prior treatment study. The subject's age at the time of screening in the prior treatment study will be used for PN017 criteria, procedures, and analyses.

1.4.1 Adult Population

Eligible adult subjects enrolled in PN017 will be followed for up to 7 study visits across 3 years (or up to 11 study visits across 5 years for subjects from prior treatment study PN052) after the prior treatment study. Additional visit(s) may be conducted for viral confirmation as determined by the investigator.

Evaluation of the adult population enrolled in PN017 will include: 1) the durability of response in subjects who had achieved SVR_{24}, 2) the development and persistence of virologic resistance, and/or 3) the progression of liver disease and co-morbid conditions in all subjects and the progression of kidney disease in subjects with CKD. Assessments evaluated for each adult subject will depend on the subject's prior treatment study and whether enrolled into this study prior to or after AM 03.

1.4.2 Pediatric Population

Eligible pediatric subjects enrolled in PN017 will be followed for up to 7 study visits across 3 years after prior treatment study PN079 to evaluate the persistence of virologic resistance. Additional visit(s) may be conducted for viral confirmation as determined by the investigator.

1.5 STUDY POPULATION

The subject's age at the time of screening for the prior treatment study will be used for PN017 criteria, procedures, and analyses.

1.5.1 Adult Population

Prior to AM 03, all HCV-infected adult subjects previously treated with GZR in a prior treatment study were eligible for enrollment into PN017.

- AM 03 limited study eligibility to HCV-infected subjects who had either: 1) failed a GZR-containing therapy in a prior treatment study or 2) had CKD and received at least 1 dose of GZR in prior treatment study PN052. Starting with AM 03, the following adult subjects were discontinued from PN017 based on the new eligibility criteria: Subjects who had achieved SVR in a prior treatment study (other than PN052).

- Subjects who had failed GZR-containing therapy in a prior treatment study and received retreatment with a different HCV therapy (either prior to or during active participation in PN017).

1.5.2 Pediatric Population

Enrollment is limited to subjects who experienced virologic failure associated with 1 or more treatment-emergent RASs present at 12 weeks after receiving GZR treatment in prior treatment study PN079.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

No treatments will be administered.

1.7 STUDY FLOW CHART

There are 2 flow charts for this study, 1 for adult subjects and 1 for pediatric subjects. The subject's age at the time of entering the prior treatment study will be used for PN017 procedures.

1.7.1 Adult Population

Visit No.	1[8]	2	3	4	5	6	7	8[13]	9[13]	10[13]	11[13]	12
		Year 1		Year 2		Year 3		Year 4		Year 5		
STUDY PROCEDURES[1]	**Screen/ Baseline[4]**	**Mo. 6**	**Mo. 12**	**Mo. 18**	**Mo. 24**	**Mo. 30**	**Mo. 36[11]**	**Mo. 42**	**Mo. 48**	**Mo. 54**	**Mo. 60[11]**	**(Unscheduled) Viral Confirmation Visit[10]**
Informed Consent	X											
Informed Consent for FBR [2]	X											
Provide Subject Identification Card	X											
Medical History [12]	X											
Inclusion/Exclusion Criteria	X											
CLINICAL EVALUATIONS												
Directed Physical Examination (PE)	X		X		X		X		X		X	X
Child-Pugh score computation	X		X		X		X		X		X	X
Blood pressure (systolic and diastolic) and heart rate	X		X		X		X		X		X	X
Weight	X		X		X		X		X		X	
Height	X											
Review procedure related AEs, ECIs, and drug-related SAEs[3]	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY SAFETY EVALUATIONS												
Chemistry, hematology, and coagulation panel	X	X	X		X		X		X		X	X
MELD score (with and without dialysis)	X		X		X		X		X		X	X
Fibrosure® (Fibrotest®)		X	X		X		X		X		X	X
eGFR (if prior treatment study was PN052)	X		X		X		X		X		X	X
HCV EVALUATIONS												
HCV RNA Level[5]	X	X	X	X	X	X	X	X	X	X	X	X
Viral Resistance and Biomarker[6]	X	X	X	X	X	X	X	X	X	X	X	X
Blood (DNA) for FBR[7]	X											
Blood (Plasma) for FBR[7]	X											
HCV Genotype[9]	X											X

Visit No.	1[8]	2	3	4	5	6	7	8[13]	9[13]	10[13]	11[13]	12
		Year 1		Year 2		Year 3		Year 4		Year 5		
STUDY PROCEDURES[1]	**Screen/ Baseline[4]**	**Mo. 6**	**Mo. 12**	**Mo. 18**	**Mo. 24**	**Mo. 30**	**Mo. 36[11]**	**Mo. 42**	**Mo. 48**	**Mo. 54**	**Mo. 60[11]**	**(Unscheduled) Viral Confirmation Visit[10]**

AE=adverse event; DNA=deoxyribonucleic acid; ECI- event of clinical interest; eGFR=estimated glomerular filtration rate; FBR=future biomedical research; HCV=hepatitis C virus; MELD=Model for End Stage Liver Disease; Mo.=month; RNA=ribonucleic acid; SAE=serious adverse event

1 Visits should be scheduled as close to the indicated study period as possible. Visit windows are +/- 3 months. All visits should be recorded on the actual date that they occur and any missed or late visits must be documented accordingly.
2 Participation in FBR is voluntary and is not required in order to participate in the study.
3 Protocol specified ECIs, AEs related to protocol-specified procedures (blood draw), and drug related new Serious Adverse Events, which occur following enrollment in the present study (after Informed Consent Form is signed) will be reported.
4 If a subject is directly entered into this long-term follow-up protocol on the same day as the last study day of the prior treatment study, since these visits have different laboratory requirements, the lab kit for each of the two visits must be used. Samples are collected for each study separately at the same visit. (See section 3.2.4.1)
5 Subjects who achieved SVR in previous study and who are tested in this study and found to have HCV RNA ≥1000 IU/mL, will have their Viral Resistance sample tested.
6 HCV sequence analysis will be performed, as appropriate, and will depend on the HCV-RNA level results.
7 Informed consent for future biomedical research samples must be obtained before the DNA and plasma samples are collected.
8 The screening visit should occur within 3 months of the last visit of the previous protocol.
9 Subjects who had HCV RNA < LLoQ at the end of follow-up in the original treatment protocol and who are tested and have HCV-RNA ≥LLoQ during this study will have their HCV Genotype obtained. If a subject has HCV RNA ≥ LLoQ at Visit 1, an HCV Genotype must be performed at that visit.
10 If the unscheduled visit is being performed for follow-up of an AE/SAE (as defined in this protocol), a directed physical exam and safety labs should also be performed at this visit.
11 For subjects in the 3 year follow-up who discontinue early, a Visit 7 (Month 36) Visit should be completed as the early discontinuation visit. For subjects in the 5 year follow-up (eg. PN052) who discontinue early, a Visit 11 (Month 60) visit should be completed as the early discontinuation visit.
12 Refer to Section 3.2.4.1 for required medical history.
13 Visits 8, 9, 10, and 11 will only be performed if subjects were in PN052 as their parent study.

1.7.2 Pediatric Population

Visit No.	1[5]	2	3	4	5	6	7	Unscheduled Visit[6]
		Year 1		Year 2		Year 3		
STUDY PROCEDURES[1]	**Screen/Baseline[4]**	**Mo. 6**	**Mo. 12**	**Mo. 18**	**Mo. 24**	**Mo. 30**	**Mo. 36[7]**	
Informed Consent/Assent	X							
Informed Consent/Assent for FBR[2]	X							
Provide Subject Identification Card	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
CLINICAL EVALUATIONS								
Directed Physical Examination	X		X		X		X	X
Weight	X		X		X		X	X
Height	X		X		X		X	X
Date of menarche (females only)	X	X	X	X	X	X	X	
Procedure Related AEs and drug-related SAEs[3]	X	X	X	X	X	X	X	X
HCV EVALUATIONS								
HCV RNA Level and sequence analysis[8]	X	X	X	X	X	X	X	X
Viral Resistance and Biomarker[8]	X	X	X	X	X	X	X	X

AE=adverse event; DNA=deoxyribonucleic acid; FBR=future biomedical research; HCV=hepatitis C virus; Mo.=month; RNA=ribonucleic acid; SAE=serious adverse event

1 Visits should be scheduled as close to the indicated study period as possible. Visit windows are +/- 3 months. All visits should be recorded on the actual date that they occur and any missed or late visits must be documented accordingly.
2 Participation in FBR is voluntary and is not required in order to participate in the study.
3 AEs related to protocol-specified procedures (blood draw) and drug related new Serious Adverse Events, which occur following enrollment in the present study (after Informed Consent Form is signed) will be reported.
4 If a subject is directly entered into this long-term follow-up protocol on the same day as the last study day of the prior treatment study, only the lab kit from prior treatment study needs to be used.
5 The screening visit should occur within 3 months of the last visit of the previous protocol.
6 If the unscheduled visit is being performed for follow-up of an AE/SAE (as defined in this protocol), only a directed physical exam is needed at this visit. If for follow-up of viral resistance, only HCV evaluations are needed.
7 For subjects who discontinue early, a Visit 7 (Month 36) should be completed as the early discontinuation visit.
8 Leftover main study plasma from HCV RNA and resistance will be stored for FBR if the subject/legally acceptable representative consents to FBR.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary

2.1.1.1 Adult Population

In HCV-infected subjects who received at least 1 dose of GZR in a previous study:

1. **Objective:** To evaluate the durability of response in subjects who achieved SVR_{24} in the prior treatment study and at the time of entry into PN017 were HCV ribonucleic acid (RNA) <lower limit of quantification (LLoQ) (either target not detected [TND] or target detected, unquantifiable [TD(u)]).

2. **Objective:** To evaluate the presence of treatment-emergent antiviral resistance to NS3/4A, NS5A and/or NS5B regions, (as applicable) and determine if there is a reversion to wild-type pattern within the 3-year time frame of this long-term follow-up study (or 5-year time frame for subjects from PN052) in subjects with virologic failure in the prior treatment study and with HCV RNA ≥1000 IU/mL in Protocol 017.

3. **Objective:** To evaluate the long-term safety.

2.1.1.2 Pediatric Population

In HCV-infected subjects who received at least 1 dose of GZR in a previous study:

1. Objective: To evaluate the persistence of treatment-emergent antiviral resistance to NS3 and NS5A regions within the 3-year time frame of this long-term follow-up study.

2.1.2 Exploratory (Adult Population Only)

1. **Objective:** To assess liver function using the Model for End-Stage Liver Disease (MELD) and/or Child-Pugh scores in all adult subjects.

2. **Objective:** To assess CKD status by assessing change in estimated glomerular filtration rate (eGFR) in subjects from PN052.

3. **Objective:** To assess complication of CKD by recording new onset diabetes, cryoglobulinemia, cardiovascular disease, and/or neurologic disorders (such as stroke) in subjects from PN052.

4. **Objective:** To assess health outcomes by recording the occurrence of variceal bleeding, ascites, spontaneous bacterial peritonitis, encephalopathy, hepatorenal syndrome, hepatocellular carcinoma, liver or kidney transplantation, and graft rejection in subjects who have undergone liver or kidney transplantation.

2.2 SUBJECT INCLUSION CRITERIA (ADULT AND PEDIATRIC POPULATIONS)

Inclusion criteria apply to both adult and pediatric populations unless otherwise noted.

1. Subjects previously participated in a HCV treatment study and received GZR in the treatment regimen.

2. Subject must enroll in PN017 (Visit 1) within 3 months of the last study visit (e.g. follow-up week [FW] 24) of the prior treatment study in which they received a GZR containing regimen.

3. Subject is male or female 3 years of age or older on day of signing informed consent/assent.

4. Subject or subject's legally acceptable representative provides written informed consent (or written informed assent where applicable). Subjects who have consented for the study may also provide consent/assent for Future Biomedical Research (FBR). However, the subject may participate in PN017 without consenting/assenting for FBR.

5. Starting with AM 03: Adult subject must have received at least 1 dose of a GZR-containing regimen in the prior treatment study and identified as having failed therapy in that study.

6. Pediatric subject must have received at least 1 dose of a GZR-containing regimen and experienced virologic failure with 1 or more associated treatment-emergent RASs at FW12 in PN079.

2.3 SUBJECT EXCLUSION CRITERIA (ADULT AND PEDIATRIC POPULATIONS)

Exclusion criteria apply to both the adult and pediatric populations.

1. **Adult subjects**: In the opinion of the investigator, subject is mentally or legally incapacitated at entry into PN017.

   Pediatric subjects: The subject has significant emotional problems or a clinically significant psychiatric disorder that may interfere with participant treatment, assessment, or compliance with the protocol.

2. Subject has received HCV therapy after completion of the prior treatment study and before entry into PN017.

3. Starting with AM 03: subjects who failed therapy due to re-infection, defined as:

   - an HCV RNA sample with a different genotype than the baseline genotype in the prior treatment study, or

- an HCV RNA sample determined to be reinfection by phylogenetic analysis with comparison to the baseline sequence in the prior treatment study.

4. Starting with AM 03: subjects who failed therapy in the prior treatment study and received retreatment with HCV therapy.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is a multicenter long-term follow-up study for subjects previously treated with at least one dose of GZR in a Merck-sponsored clinical study.

2.4.1.1 Adult Population

Prior to AM 03, all HCV-infected adult subjects previously treated with GZR in a Merck-sponsored clinical study (parent study) were eligible for enrollment into PN017.

Starting with AM 03, several significant changes have been made to the study design and duration:

1. New enrollment will be limited to those who failed therapy in the prior treatment study.

2. Subjects in PN017 with virologic failure at FW24 in the prior treatment study will continue for 3 years of follow-up (other than PN052 subjects) or 5 years of follow-up (PN052 subjects).

3. Subjects (other than PN052 subjects) in PN017 who entered with HCV RNA <LLoQ were discontinued after the next scheduled visit.

4. Subjects who receive a new HCV therapy regimen during PN017 will be discontinued.

5. The enrollment window is 3 months after the last visit in the prior treatment study.

There are a total of 7 study visits (11 study visits for PN052 subjects) and, as needed, a viral confirmation visit.

2.4.1.2 Pediatric Population

The anticipated duration is 3 years for pediatric subjects. Subject enrollment is limited to subjects from PN079 who experienced virologic failure associated with 1 or more treatment-emergent RASs present at FW12. There are a total of 7 study visits and, as needed, a viral confirmation visit. Pediatric subjects who receive a new HCV therapy regimen during PN017 will be discontinued.

2.4.2 Treatment Plan

Not applicable.

2.5 LIST OF EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY MEASUREMENTS

The following measurements are applicable for the adult and pediatric populations.

HCV Genotype

Samples will be genotyped using the Food and Drug Administration (FDA) approved Abbott HCV Real Time Genotype II assay which detects HCV GT1a, 1b, 2, 3, 4, 5, and 6 through the use of genotype-specific fluorescent-labeled oligonucleotide probes in a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay. The RT-PCR reaction uses 3 sets of HCV specific amplification primers targeting the conserved 5'untranslated region (for all genotypes) and NS5B regions from GT1a and 1b. The assay has accuracy of >96% for GT1, 1a, 1b, 2, 3 and 4, 89% for GT5 and 83% for GT6 with 100% specificity in HCV serologically negative plasma samples. Phylogenetic analyses will be performed using sequences for NS3/4A, NS5A and NS5B to ensure accurate assignment of sample genotype/subtype.

HCV RNA

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. HCV RNA definitions are presented in Table 1.

Table 1

HCV RNA Definitions

Abbreviation	Definition	HCV RNA Level
TND	Target not detected	HCV RNA not detected
TD(u)	Target detected, unquantifiable	HCV RNA < LLoQ
TD(q)	Target detected, quantifiable	HCV RNA ≥ LLoQ
HCV=hepatitis C virus; LLoQ=lower limit of quantification; RNA=ribonucleic acid		

For subjects enrolled prior to AM 03, durability of virologic response will be assessed in all subjects who are HCV RNA <LLoQ (either TND orTD[u]) on Day 1 of entry into this protocol and excluding any subject who is TND/TD(u) due to having received an anti-viral treatment after having failed previous therapy in the parent study.

Failure of therapy due to relapse more than 24 weeks after the end of therapy (termed late relapse) in this group of subjects will be measured as an HCV RNA that is confirmed to be ≥LLoQ and is not due to a new infection or re-infection. Confirmation is defined as an HCV RNA that is target detected, quantifiable (TD[q]) from a separate blood draw repeated in approximately 4 weeks.

Subjects who entered this protocol with HCV RNA TND or TD(u) and without confirmation of having failed therapy in the prior treatment study will be categorized as maintaining SVR. These subjects will be assessed for late relapse at every visit in this protocol, including the entry visit. See Table 2 below for actions and interpretations based on HCV RNA results of scheduled and viral confirmation visits.

Table 2

Actions and interpretations based on HCV RNA results of scheduled and Viral Confirmation visits

Scheduled Visit Result	Action	Result of Viral Confirmation	Interpretation
TND	None	N/A	SVR
TD(u)	None	N/A	SVR
TD(q) Not previously determined to be a relapse, e.g. first time HCV RNA ≥ LLoQ	Viral Confirmation Visit	TND/TD(u)	SVR
		≥ TDq	Relapse

HCV=hepatitis C virus; LLoQ=lower limit of quantification; RNA=ribonucleic acid; SVR=sustained virologic response; TND=target not detected; TD(q)=target detected, quantifiable; TD(u)=target detected, unquantifiable

Any relapse subject with HCV RNA ≥1000 IU/mL will have a sequence analysis performed on all samples where HCV RNA ≥1000 IU/mL.

Viral Resistance Measurements

A viral resistance sample will be collected for every subject at every visit. For subjects with HCV RNA ≥LLoQ (TD[q]) sequence analysis will be performed if HCV RNA ≥1000 IU/mL.

2.6 LIST OF SAFETY MEASUREMENTS

2.6.1 Adult Population

The long-term safety will be assessed by twice yearly study visits. Once yearly, there will be a directed physical exam and standard laboratory safety tests. Twice yearly, there will be a collection of ECIs (as specified in Section 3.4.3.2), any adverse events (AEs) related to protocol-specified procedures (blood draw), and drug-related serious adverse events (SAEs) as specified in the study flow chart in Section 1.7.1. For details on ECIs collected, see Section 3.4.3.2.

Hematologic/Chemistry Measurements

The following laboratory tests will be performed yearly:

- ***Hematology***- hemoglobin (Hgb), hematocrit (HCT), red blood cell (RBC) count, white blood cell (WBC) count, lymphocytes, neutrophils, and platelet count;
- ***Chemistry***- alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, total bilirubin (direct and indirect), urea nitrogen, total protein, albumin, and glucose;
- ***Coagulation panel***- including prothrombin time (PT), activated partial thromboplastic time (aPTT), and international normalized ratio (INR) of the prothrombin time; and
- ***Computed MELD score***- Sponsor will calculate based on available data for study visit for all adult subjects (at the time of entry in the prior treatment study).

2.6.2 Pediatric Population

The long-term safety will be assessed by twice yearly study visits. Once yearly, there will be a directed physical exam. Twice yearly, there will be a collection of any AEs related to protocol-specified procedures (blood draw) and drug related SAEs as specified in the study flow chart in Section 1.7.2. There are no ECIs or laboratory safety tests collected for the pediatric population.

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan (SAP) are summarized below; the comprehensive plan is provided in Section 3.5. The adult population and pediatric population will be summarized separately.

2.7.1 Efficacy Analyses

2.7.1.1 Adult Population

The primary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses in the adult population are presented in Table 3**.**

There will be no formal efficacy hypothesis testing conducted in this study.

The primary efficacy objectives of this study are to evaluate the durability of response in subjects who achieved SVR in the prior treatment study, as follows, and the evaluation of antiviral resistance to GZR, as described in 2.7.3.

Durability of SVR will primarily be evaluated based upon the time to viral relapse, which is defined as the time from last dose of study therapy taken in the prior treatment study until the date where HCV RNA is ≥LLoQ (see Section 2.5). The analysis population for the time to relapse analysis will be all subjects who achieved SVR during the follow-up

period of the prior treatment study and did not start any new HCV therapy between the end of the prior treatment study and entry in this study.

The distribution of time to viral relapse will be summarized using Kaplan-Meier estimates. In addition, the percentage of subjects who remain HCV RNA <LLoQ during the course of this study will be summarized.

Subjects who receive other treatments for HCV concurrently with this protocol or prior to PN017 and after completion of therapy in the prior treatment study will be discontinued from PN017, and their data excluded from analysis from the time of initiation of new therapy.

Table 3

Summary of Analysis Strategy for Key Efficacy Endpoints
(Adult Population)

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Durability of SVR (Time to viral relapse)	Kaplan-Meier plot and summary statistics	All adult subjects entered who achieved SVR in the prior treatment study and who did not start new HCV treatment between end of the prior treatment study and study entry in PN017.	Data as Observed[a]
Antiviral resistance	Descriptive statistics	RAS Analysis Population is defined as allocated adult subjects who met Virologic Failure criteria in the prior treatment study or up to entry into PN017 and who entered PN017 with TD(q) HCV RNA, excluding subjects who were reinfected or who meet any of the following criteria: Failure to receive at least 1 dose of GZR in the prior treatment study or subject had another protocol violation.	Data as Observed

GZR=grazoprevir; HCV=hepatitis C virus; LLoQ=lower limit of quantification; PN=protocol number; RAS=resistance associated substitution(s); RNA=ribonucleic acid; SVR=sustained virologic response

[a]Subjects who discontinue without relapsing will be censored at the time of discontinuation.

2.7.1.2 Pediatric Population

There will be no efficacy assessment of durability of long-term SVR in this population as enrollment in this study will be limited to pediatric subjects who were virologic failures and had treatment emergent RAS present at FW12 in the prior treatment study.

2.7.2 Safety Analyses

2.7.2.1 Adult Population

The safety analyses will be based on data from all adult subjects entering the study. Long-term safety, drug-related SAEs, ECIs, any AEs related to protocol-specified procedures (blood draw), and laboratory data will be summarized for all adult subjects using descriptive statistics. Follow-up data collected after a subject started HCV treatment will be summarized separately.

2.7.2.2 Pediatric Population

The safety analyses will be based on data from all pediatric subjects entering the study. Long-term safety, any AEs related to protocol-specified procedures (blood draw), and drug-related SAEs will be summarized for all pediatric subjects using descriptive statistics.

2.7.3 Analysis of Resistant Associated Substitutions

2.7.3.1 Adult Population

The evaluation of antiviral resistance to GZR will be obtained on subject samples with HCV RNA ≥1000 IU/mL at study entry or during the course of this study; the presence of RASs and the persistence of RASs over time will be summarized using descriptive statistics, with subgroup analyses by class of regimen (e.g. NS3/4A inhibitors, NS5A inhibitors and NS5B inhibitors) as well as by specific components (Table 3). Only subjects who experienced virologic failure (other than reinfection) will be included in these analyses.

2.7.3.2 Pediatric Population

The primary endpoints, primary analysis population, and statistical methods that will be employed for the RAS analyses in the pediatric population are presented in Table 4.

Table 4
Summary of Analysis Strategy for Resistant Associated Substitutions
(Pediatric Population)

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Antiviral resistance	Descriptive statistics	RAS Analysis Population is defined as allocated pediatric subjects who met Virologic Failure criteria in the prior treatment study with treatment emergent RAS present at follow-up Week 12, excluding subjects who were reinfected or who meet any of the following criteria: Failure to receive at least one dose of GZR in the prior treatment study or subject had another protocol violation.	Data as Observed
GZR=grazoprevir; HCV=hepatitis C virus; LLoQ=lower limit of quantification; PN=protocol number; RAS=resistance associated substitution(s); RNA=ribonucleic acid; SVR=sustained virologic response			

2.7.4 Power and Sample Size

The sample size of this study is not pre-set.

2.7.5 Interim Analysis

Annual reporting of data available may be performed, as necessary.

3. PROTOCOL DETAILS

3.1 RATIONALE

3.1.1 Rationale for This Study

For the rationale for this study refer to Section 1.3.

3.1.2 Rationale for Future Biomedical Research

Conduct of FBR applies to both adult and pediatric subjects who provided consent/assent for FBR.

Merck will conduct FBR on blood (deoxyribonucleic acid [DNA]) and blood (plasma) specimens collected during this clinical study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes. Samples may also be used for future assay development.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic (PK)/Pharmacodynamic (PD) relationships are observed or AEs are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical studies. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of the FBR sub-study are presented in Appendix 6.1. Additional informational material for institutional review boards/ethics committees (institutional review boards [IRB]/ ethical review committees [ERC]) and investigational site staff is provided in Section 7.

3.2 STUDY PROCEDURES

There are a total of 7 study visits (11 study visits for PN052 subjects) and, as needed, a viral confirmation visit.

3.2.1 Subject Population

Only adult and pediatric subjects who received at least 1 dose of GZR in a previous Merck-sponsored clinical study are eligible for enrollment in PN017. For full details on adult and pediatric subjects eligible for enrollment in this study, refer to Sections 2.4.1.1 and 2.4.1.2, respectively.

3.2.2 Concomitant Medication(s)/Treatment(s)

3.2.2.1 Adult Population

In the original protocol, subjects were permitted to participate in other treatment studies for HCV concurrently with this protocol.

Starting with AM 03, subjects are not permitted to receive any therapies used for the treatment of HCV concurrently with this protocol.

3.2.2.2 Pediatric Population

Pediatric subjects enrolled in this study are required to discontinue from the study if they receive any HCV therapy.

3.2.3 Diet/Activity/Other

There are no dietary or activity restrictions for this study.

3.2.4 Procedures

Unless otherwise noted, the procedures described below apply to both adult and pediatric subjects.

Procedures visits should be scheduled as close to the indicated study weeks as possible but must be performed within +/- 3 months. Refer to the Study Flow Charts in Section 1.7 for a complete listing of study procedures required at each study visit.

3.2.4.1 Screening/Baseline Visit (Visit 1)

Within 3 months of the last visit (e.g. FW24) of their prior treatment study, potential subjects will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as described in Sections 2.2 and 2.3, respectively. The investigator will discuss with each potential subject the nature of the study, its requirements, and its restrictions. Informed consent/assent, as described below, must be obtained prior to initiation of any screening/baseline procedures or evaluations.

All procedures must be completed and subject eligibility confirmed by the investigator prior to the subject receiving an allocation number by the study site.

Electronic transfer of data from the prior treatment study will occur for the following data:

- Dosage and length of therapy (start date/end date) of GZR from the prior treatment study
- All HCV RNA
- Date declared relapse in prior treatment study (if applicable)
- HCV Genotype

- All sequence analysis

- All laboratory results:
    - Hemoglobin
    - Hematocrit
    - Red Blood Cell Count
    - Total White Blood Cell count
    - Lymphocytes
    - Neutrophils
    - Platelet Count
    - ALT
    - AST
    - Creatinine
    - eGFR (if prior treatment study was PN052)
    - Alkaline phosphatase
    - Total Bilirubin (direct and indirect)
    - Urea nitrogen
    - Total Protein
    - Albumin
    - Glucose
    - Coagulation panel: PT, INR and aPTT

In addition, the following information will be collected at the screening/baseline visit and must be manually entered into the data collection system:

- Protocol number and subject allocation number from the prior treatment study.

- Name, dosages and length of therapy (start date/end date) of all other HCV therapies including other research protocols or standard of care.

- For adult subjects, the following medical history terms, which occurred after the prior treatment study and before study entry, will be collected:
    - Spontaneous bacterial peritonitis;
    - Variceal bleeding;
    - Ascites;
    - Encephalopathy;
    - Hepatorenal syndrome;
    - Hepatocellular carcinoma (collected as an ECI);
    - Change in chronic kidney disease as assessed by eGFR (collected as an ECI);
    - Liver transplant;
    - Kidney transplant (PN052 subjects; collected as an ECI);
    - New onset diabetes, cryoglobulinemia, cardiovascular disease limited to new onset angina, myocardial infarction, or neurologic disorders limited to transient ischemic attack (TIA) or stroke;

- Graft rejection in subjects who have undergone liver or kidney transplantation; and
- Post transplantation glomerulonephritis.

In some cases, the subject may have a combined visit (the initial visit for PN017 occurs on the same day as the last study day of the prior treatment study). For adult subjects, the lab kit from each study for its designated visit must be used so that samples are collected for each study separately at the same visit. For pediatric subjects, only one lab kit is required as there are no additional tests for PN017.

All subjects will be given a card, at the time of screening, identifying them as subjects in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

3.2.4.2 Informed Consent/Assent (Adult and Pediatric Populations)

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

3.2.4.2.1 General Informed Consent/Assent

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

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

The initial informed consent/assent form, any subsequent revised written informed consent/assent form and any written information provided to the subject/legally acceptable representative must receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject'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 subject's dated signature or by the subject's legally acceptable representative's dated signature.

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

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

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

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

The following specimens are to be obtained as part of FBR for adult subjects:

- Blood (DNA) for genomics use; and
- Blood (Plasma) for FBR

For pediatric subjects, leftover plasma may be used for FBR only if the subject/legally acceptable representative signed for FBR consent/assent.

3.2.4.3 Assignment of Baseline (Screening) Number (Adult and Pediatric Populations)

For identification purposes during the pre-study (screening) period, each subject will be assigned a unique baseline (screening) number from the group of numbers provided by the SPONSOR. Once a baseline number has been assigned to a subject, the baseline number should not be reassigned for any reason. If a subject needs to be rescreened for any reason, the same baseline number will be used.

3.2.4.4 Randomization/Allocation (Adult and Pediatric Populations)

Subjects will not be randomized in this study. Subjects will be assigned an allocation number by interactive voice/web response system (IXRS).

A single subject cannot be assigned more than 1 allocation number.

3.2.4.5 Years Post Entry Into Study, Years 1 through 3 (Visits 2 through 7): Adult and Pediatric Populations

All procedures for Visits 2 through 7 should be performed for adult and pediatric subjects entering the study as indicated on the Study Flow Charts in Section 1.7.1 and Section 1.7.2, respectively. After initiation of AM 03, not all subjects will complete all visits through Visit 7.

3.2.4.6 Years 4 and 5 Post Entry (Visit 8 through 11): Adult Population

Subjects from PN052 will have a year 4 and year 5 visit.

With initiation of AM 03, follow-up beyond year 3 will no longer be necessary for subjects enrolling from PN059.

3.2.4.7 Treatment/Evaluation/Follow-Up

Not applicable. This is a long-term follow-up study and no treatments will be administered.

3.2.4.8 Discontinuation/Withdrawal from Study (Adult and Pediatric Populations)

Subjects may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject has been discontinued/ withdrawn due to an adverse experience (telephone or FAX). When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.

3.2.4.8.1 Discontinuation/Withdrawal Criteria

With the exception of subjects previously enrolled in PN052, if a subject is discontinued early from the study the subject should complete their last visit as Visit 7 (Month 36). If a subject from PN052 is discontinued early from the study, the subject should complete their last visit as Visit 11 (Month 60).

A subject will be discontinued from the study for any of the following reasons:

- The Investigator feels that it is in the best interest of the subject to discontinue.
- Request of the subject/subject's legally acceptable representative (subject/subject's legally acceptable representative has the right to discontinue from the study at any time for any reason).
- Following AM 03 all subjects (except PN052) who entered PN017 with HCV RNA TND or TD(u) were discontinued. For these subjects, participation was discontinued at the next scheduled visit for each subject.
- Following AM 03, all subjects who initiated HCV treatment after enrollment in PN017 were discontinued.

3.2.4.9 Withdrawal From Future Biomedical Research (Adult and Pediatric Populations)

Subjects may withdraw their consent/assent for FBR and have their specimens and all derivatives destroyed. Subjects/subject's legally acceptable representative may withdraw consent/assent at any time by writing to the principal investigator for the main study. If medical records for the main study are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete

specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

3.3 DURABILITY, VIRAL RESISTANCE, AND SAFETY MEASUREMENTS

3.3.1 Clinical and Laboratory Measurements for Durability, Viral Resistance, and Safety

3.3.1.1 Adult Population

The primary measurement for durability of response in this study is repeat HCV RNA measurements at all study visits. Resistance will be assayed by sequence analysis, and safety will be assessed by directed physical exam, standard laboratory safety tests, and collection of ECIs, any AEs related to protocol-specified procedures (blood draw), and drug related SAE's at each visit as specified in the study flow chart in Section 1.7.1.

Clinical Evaluations

- Directed Physical Examination: Yearly as described in the flow chart.
    - The examination must be performed by the Principal Investigator or Sub-Investigator (physician, physician assistant or nurse practitioner) listed on FDA Form 1572 *or equivalent document.*
- Collection of therapies used for the treatment of HCV**:** All visits.

  NOTE: Following AM 03, all subjects who initiated HCV treatment after enrollment in PN017 were discontinued.
- Childs-Pugh Score: Computed from safety laboratory data and clinical assessment obtained at baseline and every year for adult subjects
    - http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality/
- Blood pressure and heart rate
- Weight and height

- Review procedure related AEs, ECIs, and drug-related SAEs

Unscheduled Visits:

- Unscheduled visits may be performed at any time at the discretion of the Investigator.

Laboratory Safety Evaluations

The following will be collected (as defined in Section 2.6.1):

- Chemistry (Abbreviated Non-fasting), hematology, and coagulation panel-collected yearly, with an additional collection at 6 months;

- MELD score (with and without dialysis): Computed from safety laboratory data obtained at baseline, and every year for all adult subjects (at the time of entry in the prior treatment study).

- Fibrosure® (Fibrotest®) - collected at 6 months post study entry and then yearly beginning at 12 months in all adult subjects (at the time of entry in the prior treatment study); and

- eGFR (collected yearly in PN052 subjects only).

HCV Evaluations

- HCV RNA quantitation - collected at all visits;

    - If any subject's HCV-RNA result is increased from prior HCV RNA result (e.g. previously TND and now TD[u] or ≥LLoQ), the subject will be asked to return to the clinic within 14 days for a Viral Confirmation Visit (Visit 8). Various scenarios, actions, and interpretations are described in Table 5 below.

    - Plasma samples for HCV-RNA must be obtained and processed as instructed by the central laboratory.

- HCV Viral Resistance and Biomarker: Collected at all visits, tested as appropriate.

    - HCV population sequence analysis will be conducted, as appropriate to evaluate the presence of HCV resistance associated substitutions in NS3/4A, NS5A, or NS5B as appropriate and based on the regimen they received in the prior treatment study. Sequence analysis will be performed on any sample with HCV RNA >1000 IU/mL using the viral resistance samples that are collected and stored at every visit.

- Protein, RNA levels, metabolites, bile acids, and other markers of disease may be measured from blood samples to compare biomarkers measured during the prior treatment study to biomarkers measured at various time points during this protocol. An example of a method that may be used to measure protein levels is mass spectrometry. Plasma samples will be digested into peptides by proteases. These peptides will then be measured by mass spectrometry to determine the sequence and/or abundance of tens of thousands of peptides. The pattern of peptides will be compared between subjects who respond to drug treatment and subjects who do not respond to treatment. In addition to mass spectrometry, standard immunoassays for protein characterization such as enzyme-linked immunosorbent assays may be used to characterize levels of specific proteins identified by the mass spectrometry analysis. RNA levels will be measured in blood samples by array hybridization and/or by Polymerase Chain Reaction. Metabolites will be measured by mass spectrometry or other standard assays to identify and/or quantify thousands of metabolites in plasma. For all of the plasma biomarkers measured, associations between relapse or response to drug treatment and biomarker levels will be assessed.

- FBR Sample: Screening/Baseline visit for adult subjects who provided consent.

- HCV GT: Collected at Baseline (if HCV RNA >LLoQ) and Viral Confirmation Visit.

    - If a subject achieved SVR at the end of follow-up in the prior treatment study and, is tested and found to have HCV RNA quantifiable during this study, that first sample with quantifiable HCV RNA will be tested for HCV GT. This is performed to determine if this is a relapse of the primary infection or a re-infection.

    - Plasma samples for HCV GT must be obtained and processed as instructed by the central laboratory.

Table 5

Actions and Interpretations Based on HCV RNA Results of Scheduled and Viral Confirmation Visits

Scheduled Visit Result	Action	Result of Viral Confirmation	Interpretation
TND	None	N/A	SVR
TD(u)	None	N/A	SVR
TD(q) Not previously determined to be a relapse, e.g. first time HCV RNA quantifiable	Viral Confirmation Visit	TND/TD(u)	SVR
		HCV RNA quantifiable	Relapse

HCV=hepatitis C virus; N/A=not applicable; RNA=ribonucleic acid; SVR=sustained virologic response; TND=target not detected; TD(q)=target detected, quantifiable; TD(u)=target detected but unquantifiable

Blood volumes collected at each visit are detailed in Appendix 6.2.1.

3.3.1.2 Pediatric Population

To assess persistence of virologic resistance, HCV RNA measurements will be taken at all study visits and resistance will be assayed by sequence analysis. Safety will be assessed by directed physical exam and collection of any AEs related to protocol-specified procedures and drug-related SAEs at each visit as specified in the study flow chart in Section 1.7.2.

Clinical Evaluations

- Directed Physical Examinations: Yearly as described in the flow chart.
    - The examination must be performed by the Principal Investigator or Sub Investigator (physician, physician assistant or nurse practitioner) listed on FDA Form 1572 or *equivalent document*.
- Weight and height
- Date of menarche (females only)
- Review procedure-related AEs and drug-related SAEs

Unscheduled Visits:

- Unscheduled visits may be performed at any time at the discretion of the Investigator.

HCV Evaluations

- HCV RNA quantitation – collected at all visits
    - Plasma samples for HCV-RNA must be obtained and processed as instructed by the central laboratory.
- HCV Viral Resistance and Biomarker – collected at all visits, tested as appropriate.
    - HCV sequence analysis will be conducted, as appropriate, to evaluate the presence of HCV RASs in NS3/4A or NS5A as appropriate and based on the regimen they received in the prior treatment study. Sequence analysis will be performed on any sample with HCV RNA >1000 IU/mL using the viral resistance samples that are collected and stored at every visit.
    - If consent/assent is obtained, protein, RNA levels, DNA, metabolites, bile acids, and other markers of disease may be measured from blood samples to compare biomarkers measured during the prior treatment study to biomarkers measured at various time points during this protocol.

Blood volumes collected at each visit are detailed in Appendix 6.2.2.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

3.4.1.1 Adult Population

The long-term safety will be assessed by directed physical exam, standard laboratory safety tests, and collection of ECIs, AEs related to protocol-specified procedures (blood draw), and drug related SAE's at each visit as specified in the Study Flow Chart 1.7.1.

3.4.1.2 Pediatric Population

The long-term safety will be assessed by directed physical exam and collection of AEs related to protocol-specified procedures and drug-related SAEs at each visit as specified in the Study Flow Chart 1.7.2.

3.4.2 Recording Adverse Experiences (Adult and Pediatric Populations)

ECIs, as described in Section 3.4.3.2 will be collected in the adult population. In addition, any AEs related to protocol-specified procedures (blood draw) will be collected in adult and pediatric populations. All other AEs will not be collected in this long term follow-up study.

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an AE.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

AEs may occur in the course of the use of a Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

AEs may also occur in screened subjects during any preallocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Such events will be recorded at each examination on the AE case report form (CRF)/Worksheets.

3.4.3 Immediate Reporting of Adverse Events to the SPONSOR

3.4.3.1 Serious Adverse Events (Adult and Pediatric Populations)

The following will be collected during the study:

- Drug related SAEs.
- All deaths of any cause will be collected.
- Any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All subjects with SAEs must be followed for outcome.

Note: Any drug-related SAE, or death due to any cause, which occurs to a subject must be reported within 24 hours to one of the individual(s) listed on the contact information page.

3.4.3.2 Events of Clinical Interest

3.4.3.2.1 Adult Population

ECIs will be recorded on the AE CRFs/Worksheets. ECIs defined for this protocol include:

- Spontaneous bacterial peritonitis;
- Variceal bleeding;
- Ascites;
- Encephalopathy;
- Hepatorenal syndrome;
- Hepatocellular carcinoma; - Any hepatocellular carcinoma that occurred and was not previously reported in the prior treatment study should be reported as an ECI;
- Liver transplant;
- Kidney transplant (PN052 subjects only) – any kidney transplant that occurred and was not previously reported in the prior treatment study should be reported as an ECI;
- Decreased eGFR calculated by the Modification of Diet in Renal Disease equation (PN052 subjects will be analyzed for change from baseline in PN052);
    - For this study a decrease in eGFR is defined for subjects not on dialysis as:
        - CKD4 (15 to 30 ml/min/1.73 m^2) in PN052 and is now CKD5 (<15 ml/min/1.73 m^2),
        - CKD5 without dialysis in PN 052 and is now CKD5 with dialysis, OR
        - CKD4 in PN 052 and initiates dialysis
- New onset diabetes (PN052 subjects only);
- Cryoglobulinemia (PN052 subjects only);
- Cardiovascular disease limited to angina and myocardial infarction;
- Neurologic disorders limited to TIA or stroke;
- Graft rejection in subject who has undergone liver or kidney transplantation; or
- Post transplantation glomerulonephritis (PN052 subjects only).

3.4.3.2.2 Pediatric Population

No ECIs are defined for pediatric subjects and will not be collected.

3.4.4 Evaluating Adverse Events (Adult and Pediatric Populations)

Refer to Table 6 for instructions in evaluating AEs.

Table 6

Instructions for Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	†Results in death; or	
	†Is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†Results in or prolongs an existing inpatient 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	†Is a congenital anomaly/birth defect (in offspring of subject/patient taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional.) Any overdose whether or not associated with an adverse experience must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test drug to be discontinued?	
Relationship to test drug	Did the test drug cause the adverse experience? The determination of the likelihood that the test drug caused the adverse experience 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 drug and the adverse experience based upon the available information. **The following components are to be used to assess the relationship between the test drug and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience (AE):	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test drug 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 test drug? Is the time of onset of the AE compatible with a drug-induced effect?
	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

Relationship to test drug (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the dose of test drug discontinued or 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 test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the subject/patient reexposed to the test drug in this study? 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 study is a single-dose drug study.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug 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.		
Record one of the following:		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship).**
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Definitely related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
	Probably related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of drug relationship		Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Probably not related	There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

3.4.5 SPONSOR Responsibility for Reporting Adverse Events (Adult and Pediatric Populations)

All AEs will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with International Committee on Harmonisation [ICH] Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate SAP will be issued for this study.

3.5.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This study is being conducted as a long-term follow-up study during which no study treatment will be administered.

3.5.2 Estimation

Objectives of the study are stated in Section 2.1.

3.5.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

3.5.3.1 Efficacy and RAS Endpoints

3.5.3.1.1 Adult Population

The primary efficacy endpoint in the adult population is the durability of long-term SVR which will be evaluated based upon the time to viral relapse. Viral relapse is defined as any subject who has confirmed HCV RNA ≥LLoQ and had achieved SVR in the follow-up in the prior treatment study (see Section 2.5). Relapse would be indicated so long as this was the same genotype of the virus seen in the prior treatment study (e.g. not a new infection or re-infection (see Section 2.5). Time to relapse is defined as the time from last dose of study therapy taken in the prior treatment study until the date where HCV RNA is ≥LLoQ. The percentage of subjects who remain HCV RNA <LLoQ during the course of this study will also be estimated.

In adult subjects with HCV RNA ≥1000 IU/mL at entry or during the study period, HCV sequence analysis will be performed to evaluate the presence of RASs and the persistence of RASs over time.

3.5.3.1.2 Pediatric Population

There will be no efficacy assessment of durability of long-term SVR in this population as enrollment in this study will be limited to pediatric subjects who were virologic failures and had emergent RAS present at FW12 in the prior treatment study.

In pediatric subjects, HCV sequence analysis will be performed to evaluate the presence of RASs and the persistence of RASs over time.

3.5.3.2 Safety Endpoints

3.5.3.2.1 Adult Population

Safety and signs of disease progression are assessed for all adult subjects by physical examination, drug-related SAEs, ECIs, any AEs related to protocol-specified procedures (blood draw), and laboratory tests.

3.5.3.2.2 Pediatric Population

The safety analyses will be based on data from all pediatric subjects entering the study. Long-term safety assessments include any AEs related to protocol-specified procedures (blood draw) and drug-related SAEs.

3.5.4 Analysis Populations

3.5.4.1 Efficacy Analysis and RAS Populations

3.5.4.1.1 Adult Population

The analysis population for the time to relapse analysis will be all adult subjects who achieved SVR and were not a virologic failure in the prior treatment study nor received a new HCV therapy after completing treatment with a GZR containing regimen in the prior treatment study.

HCV sequence substitutions will be evaluated in adult subjects who sign an informed consent for this study and have HCV RNA ≥1000 IU/mL at study entry and/or at any visit during the study period.

3.5.4.1.2 Pediatric Population

All pediatric subjects included in the study will be evaluated for RASs. There will be no efficacy assessment of durability of long-term SVR in this population as enrollment in this study will be limited to pediatric subjects who were virologic failures and had emergent RAS present at FW12 in the prior treatment study.

3.5.4.2 Safety Analysis Populations

3.5.4.2.1 Adult Population

All data from adult subjects who sign an informed consent/assent for this study will be included in the safety evaluation.

3.5.4.2.2 Pediatric Population

All data from pediatric subjects who sign an informed consent/assent for this study will be included in the safety evaluation.

3.5.5 Statistical Methods

No hypothesis testing will be performed in this non-drug long-term follow-up study. Efficacy and safety data will be summarized using descriptive statistics. As subjects are permitted to participate in other treatment studies for HCV concurrently with this protocol, all follow-up data collected after subjects started HCV treatment will be summarized separately.

3.5.5.1 Statistical Methods for Efficacy Analyses

3.5.5.1.1 Adult Population

The efficacy endpoint of time to viral relapse will be summarized using Kaplan-Meier methodology at fixed time points (6-month intervals). These time points represent the follow-up time since the last dose of study therapy taken in the prior treatment study. Subjects who do not relapse during the current study will be censored on the last visit date. Any subject who relapsed between the end of the prior treatment study and entry into this study will be considered a relapse at the time of study entry.

Relative days ranges, calculated from the date of last dose of therapy taken in the prior treatment study, will be used to define the months of follow-up for the analysis of time to viral relapse. These relative day ranges will be continuous and stretch from the date of last dose in the prior treatment study to the midpoint between the first 2 time points (i.e. 6 and 12 months --> midpoint: 9 months), from midpoint to midpoint between each successive pair of time points and above the last midpoint for the last time point. As the screening visit could occur within 1-year of the last dose of therapy taken in the prior treatment study for subjects enrolled prior to AM 03, certain subjects may have a follow-up time close to 6 years. Day ranges are therefore defined up to Month 72 and are provided in Table 7.

Table 7

Definition of Months of Follow-up for Time to Relapse Analysis

Month	Relative Day Range[a]
6	1 to 274
12	275 to 456
18	457 to 638
24	639 to 821
30	822 to 1003
36	1004 to 1186
42	1187 to 1368
48	1369 to 1550
54	1551 to 1733
60	1734 to 1915
66	1916 to 2098
72	≥ 2098

[a] Day range relative to date of last dose of therapy taken in the prior treatment study.

Missing Values

Only observed data will be included in the analyses. For the time to relapse analysis, subjects missing an HCV RNA evaluation at any particular visit will be considered a non-relapser for that visit. Subjects who discontinue the study without relapsing will be censored at the time of discontinuation.

3.5.5.1.2 Pediatric Population

There will be no efficacy assessment in this population as enrollment in this study will be limited to pediatric subjects who were virologic failures and had emergent RAS present at FW12 in the prior treatment study.

3.5.5.2 Statistical Methods for Safety Analyses

3.5.5.2.1 Adult Population

Safety and tolerability in adult subjects will be assessed by clinical review of all relevant parameters including drug-related SAEs, ECIs, and laboratory parameters.

The number and proportion of subjects with ECIs will be tabulated. Continuous laboratory parameters will be summarized by 12-month intervals using descriptive statistics. These 12-months intervals are related to the Study Months and are determined by a set of continuous relative day ranges, calculated from study entry. Day ranges for safety evaluation are provided in Table 8.

Table 8

Definition of Study Months for Safety Evaluation

Month	Relative Day Range[a]
Screening/Baseline	-91 to 30
12	-31 to 547
24	548 to 912
36	913 to 1277
48	1278 to 1642
60	≥1643
[a] Day range relative to study entry, i.e. date of screening/baseline visit	

Yearly changes from baseline in MELD and Child-Pugh scores will be summarized in all adult subjects using descriptive statistics. Changes in eGFR will be summarized for subjects from PN052. Descriptive statistics will be provided for the rate that subjects with CKD (PN052) require liver and/or kidney transplants.

Missing values will be handled using the Data-As-Observed approach.

3.5.5.2.2 Pediatric Population

AEs related to protocol-specified procedures (blood draw), and drug-related SAEs will be tabulated for all pediatric subjects using descriptive statistics (number and proportion).

3.5.5.3 Analysis of Resistance Associated Substitutions

3.5.5.3.1 Adult Population

HCV sequence substitutions for adult subjects will be summarized using descriptive statistics. A Kaplan-Meier method may be used to estimate the rate of return of individual resistance mutations to wild type, with subgroup analyses by class of regimen (e.g. NS3/4A inhibitors, NS5A inhibitors and NS5B inhibitors) as well as by specific components. All data collected after a subject started HCV treatment will be summarized separately.

3.5.5.3.2 Pediatric Population

The evaluation of antiviral resistance to EBR and GZR in the pediatric population will be analyzed separately from the adult population. A Kaplan-Meier method may be used to estimate the rate of return of individual resistance mutations to wild type, with subgroup analyses for both NS3/4A and NS5A RASs.

3.5.5.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized separately by adult and pediatric populations.

The number and percentage of subjects enrolled, completed, discontinued and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, race), medical history, concomitant therapies and IL28 genotype will be summarized either by descriptive statistics or categorical tables. The percentage of subjects whose HCV RNA was TD(q) at the end of the prior treatment study, at Visit 1 and at study entry will also be provided. HCV RNA at study entry is defined as HCV RNA of Visit 1 if available, otherwise the RNA assessment at the last visit in the prior treatment study provided this last visit is no more than 3 months prior to the first visit of PN017.

All demographic and baseline characteristics will be summarized for the overall population and for subjects with detectable (TD(q)) or <LLoQ HCV RNA at study entry.

3.5.6 Multiplicity

No adjustments for multiplicity are planned for this follow-up study.

3.5.7 Sample Size and Power Calculations

The sample size is not determined by any statistical considerations and is not pre-set.

3.5.8 Subgroup Analyses and Effects of Baseline Factors

The time to viral relapse in adult subjects will be summarized for categories of classification variables, shown to be associated with response such as genotype. Time to viral relapse and antiviral resistance will be summarized based upon the prior treatment study in which GZR was administered.

3.5.9 Interim Analyses

Annual reporting of data available may be performed, as necessary. Demographic, efficacy and safety data available in the database by a specified cut-off date will be summarized.

3.5.10 Compliance (Medical Adherence)

Not applicable as there is no study treatment administered.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

There are no clinical drug supplies for this study.

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 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/ERC), 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 study 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.

4.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/CRF data. By signing the consent/assent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the subject 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 subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time.

4.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub investigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the SPONSOR, and subsidiaries, affiliates and agents of the SPONSOR, in your country and

other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain SAEs to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is attached.

The investigator also agrees to allow monitoring, audits, IRB/ IEC review, and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPONSOR as a result of an audit to cure deficiencies in the study documentation and worksheets/CRFs.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/CRFs, advertising for subject participation, AE reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent/assent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality

control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying study and/or subject files.

ICH GCP guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an European Union country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (protocol Coordinating Investigator [CI]), responsible for coordinating the work of the principal investigators at the different study sites in that Member State, according to national regulations. For a single-center study, the protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study (CSRCI). The Sponsor may consider one or more factors in the selection of the individual to serve as the protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The protocol CI must be a participating study investigator.

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

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

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

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

Financial Disclosure requirements are outlined in the US FDA Regulations, Financial Disclosure by Clinical Investigators (Title 21 Code of Federal Regulations [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/sub investigator's responsibility to comply with any such request.

The investigator/sub investigator(s) agree, if requested by the Sponsor in accordance with Title 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 further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. This requirement also extends to sub investigators. The investigator also consents 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.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOP) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

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 study is solely responsible for determining whether the study is subject to requirements for submission to http://clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAAA, the EMA clinical trials directive or other mandated registries are that of the SPONSOR and agrees not to submit any information about this study to those registries.

4.6 PUBLICATIONS

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The SPONSOR will work with the authors to submit a manuscript describing study results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine studies. However, manuscript submission timelines may be extended on overt-the-counter studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later. These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the CSR, subject to the confidentiality agreement.

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. Significant contributions to study execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend the integrity of the data, method(s) of data analysis, and the scientific content of the manuscript.

The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 45 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

5. LIST OF REFERENCES

[1] Pawlotsky JM. Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens. Gastroenterology. 2016 Jul;151(1):70-86.

[2] Martinot-Peignoux M, Stern C, Maylin S, Ripault M-P, Boyer N, Leclere L, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology 2010;51(4):1122-6.

[3] Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology 2013;144(7):1450-5e2.

[4] Food and Drug Administration (CDER). Chronic hepatitis C virus infection: developing direct-acting antiviral drugs for treatment - guidance for industry [Internet]. Washington, D.C.: U.S. Department of Health and Human Services; 2016. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf.

[5] Sarrazin C. The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hepatol. 2016 Feb;64(2):486-504.

[6] Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US Population: Third national health and nutrition examination survey. Am J Kidney Dis 2003;41(1):1-12.

6. APPENDICES

6.1 COLLECTION AND MANAGEMENT OF SPECIMENS FOR FUTURE BIOMEDICAL RESEARCH

6.1.1 Scope of Future Biomedical Research

The DNA and plasma specimens collected in the current study will be used to study various causes for how subjects may respond to a drug. The DNA and plasma specimens will be stored to provide a resource for future studies conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease. Samples may also be used for future assay 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, 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

6.1.2 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 response.[2]

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

6.1.3 Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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[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.

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

b. Informed Consent/Assent

Informed consent/assent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a study visit by the investigator or his or her designate. Informed consent/assent for FBR should be presented to the subjects on Visit 1. If delayed, present consent/assent at next possible Subject Visit. Informed consent/assent forms must be obtained prior to collection of all FBR specimens.

Subjects are not required to participate in the FBR sub-study in order to participate in the main study.

Consent/assent forms signed by the subject will be kept at the clinical study site under secure storage for regulatory reasons. Information contained on the consent/assent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Subjects who decline to sign the Future Biomedical Research informed consent/assent will not have the specimen collected nor will they be discontinued from the main study.

A template of each study site's approved informed consent/assent will be stored in the Sponsor's clinical document repository. Each consent/assent will be assessed for appropriate specimen permissions.

Each informed consent/assent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. electronic Case Report Forms (eCRFs) Documentation for FBR Specimens

Documentation of both consent/assent and acquisition of Future Biomedical Research specimens will be captured in the eCRFs. Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-study's research purposes. Any specimens for which such an informed consent/assent cannot be verified will be destroyed.

d. FBR Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other study purposes.

Specimens will be collected and sent to the laboratory designated for the study where they will be processed (e.g., DNA or RNA extraction, etc.) following the Merck approved policies and procedures for specimen handling and preparation.

6.1.4 Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with FBR specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject 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 FBR, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical site, unique codes will be placed on the FBR specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the study to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by health authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the health authority.

6.1.5 Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the FBR specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-study. FBR specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6.1.6 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent/assent for FBR and have their specimens and all derivatives destroyed. Subjects may withdraw consent/assent at any time by writing to the principal investigator for the main study. If medical records for the main study are still available, the Investigator will contact MERCK using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by MERCK to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from MERCK to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

6.1.7 Retention of Specimens

FBR specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental agency 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 site will be shipped to a central laboratory and then shipped to the Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

6.1.8 Data Security

Separate databases for specimen information and for results from the FBR sub-study will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical study database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized sponsor and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for FBR purposes only as specified in this sub-study will not be used for any other purpose.

6.1.9 Reporting of FBR Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to study subject. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation, and absence of good clinical practices standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical study is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical study, Merck will publish the results without revealing specific subject information, inform all sites who participated in the Merck clinical study, and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., Disease societies who have primary interest in the results) in order that physicians and subjects may pursue clinical diagnostic testing if they wish to do so.

6.1.10 Gender, Ethnicity, and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical studies for FBR. When studies with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

6.1.11 Risks Versus Benefits of Future Biomedical Research

For FBR, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main study.

Merck has developed strict security, policies and procedures to address subject 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be reassociated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from FBR will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

6.1.12 Self-Reported Ethnicity

Subjects who participate in FBR will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in FBR.

6.1.13 Questions

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

6.2 BLOOD VOLUMES COLLECTED

6.2.1 Adult Blood Volumes

Test	Screening	Screening [a]	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42[b]	Month 48[b]	Month 54[b]	Month 60[b]
Coagulation	2.7	.	2.7	2.7	.	2.7	.	2.7	.	2.7	.	2.7
Chemistry (complete)	6	.	6	6	.	6	.	6	.	6	.	6
FibroTest	.	.	6	6	.	6	.	6	.	6	.	6
Hematology	2	.	2	2	.	2	.	2	.	2	.	2
HCV Genotype	4	.	.	.	.	.	.		.	.	.	.
HCV RNA Level	10	.	10	10	10	10	10	10	10	10	10	10
HCV Viral Resistance/RAS	6	.	6	6	6	6	6	6	6	6	6	6
Plasma for FBR	.	10	.	.	.	.	.	.	.	.	.	.
DNA for FBR	.	8.5	.	.	.	.	.	.	.	.	.	.
Total Volume in mL	**30.7**	**18.5**	**32.7**	**32.7**	**16**	**32.7**	**16**	**32.7**	**16**	**32.7**	**16**	**32.7**

DNA=deoxyribonucleic acid; FBR=future biomedical research; HCV=hepatitis C virus ; RAS= resistance associated substitution; RNA=ribonucleic acid

[a] FBR consented subjects only.
[b] Month 42 through Month 60 visits are for Protocol 052 subjects only.

6.2.2 Pediatric Blood Volumes

Test	Screening	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
HCV RNA Level	4	4	4	4	4	4	4
HCV Viral Resistance/RAS	4	4	4	4	4	4	4
Total Volume in mL	**8**	**8**	**8**	**8**	**8**	**8**	**8**
HCV=hepatitis C virus; RAS= resistance associated substitution; RNA=ribonucleic acid							

6.3 LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AM	Amendment
aPTT	Activated partial thromboplastic time
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CI	Coordinating Investigator
CKD	Chronic kidney disease
CRF	Case report form
CSR	Clinical study report
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EBR	Elbasvir; MK-8742
ECI	Event of clinical interest; selected adverse experiences
eCRF	Electronic case report forms
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ERC	Ethical review committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FW	Follow-up week
GCP	Good Clinical Practice
GT	Genotype
GZR	Grazoprevir; MK-5172
HCT	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
IB	Investigators brochure

Abbreviation/Term	Definition
ICH	International Committee on Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
IXRS	Interactive voice/web response system
LLoQ	Lower limit of quantification
MELD	Model for End-Stage Liver Disease
NS	Nonstructural protein
PD	Pharmacodynamic
PGt	Pharmacogenetics
PK	Pharmacokinetic
PN	Protocol number
PR	Pegylated-interferon + RBV
PT	Prothrombin time
RAP	Resistance associated polymorphisms
RAS	Resistance associated substitution
RBC	Red blood cell
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase-polymerase chain reaction
RZR	Ruzasvir; MK-8408
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedures
SVR	Sustained virologic response
SVR_{12}	Sustained virologic response 12 weeks after the end of all study therapy. The subject has HCV RNA < LLOQ [either TD (u) or TND] 12 weeks after the end of all study therapy
SVR_{24}	Sustained virologic response 24 weeks after the end of all study therapy. The subject has HCV RNA < LLOQ [either TD (u) or TND] 24 weeks after the end of all study therapy

Abbreviation/Term	Definition
TD(q)	Target detected, quantifiable
TD(u)	Target detected, unquantifiable
TIA	Transient ischemic attack
TND	Target not detected
UPR	Uprifosbuvir; MK-3682
US	United States
WBC	White blood cell

7. ATTACHMENTS

7.1 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 subject 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 (e.g., 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 subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects 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 subjects, 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. Subject Protection

A. IRB/ERC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects 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 subject 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 subject 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 subjects 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 subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

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/ERC 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

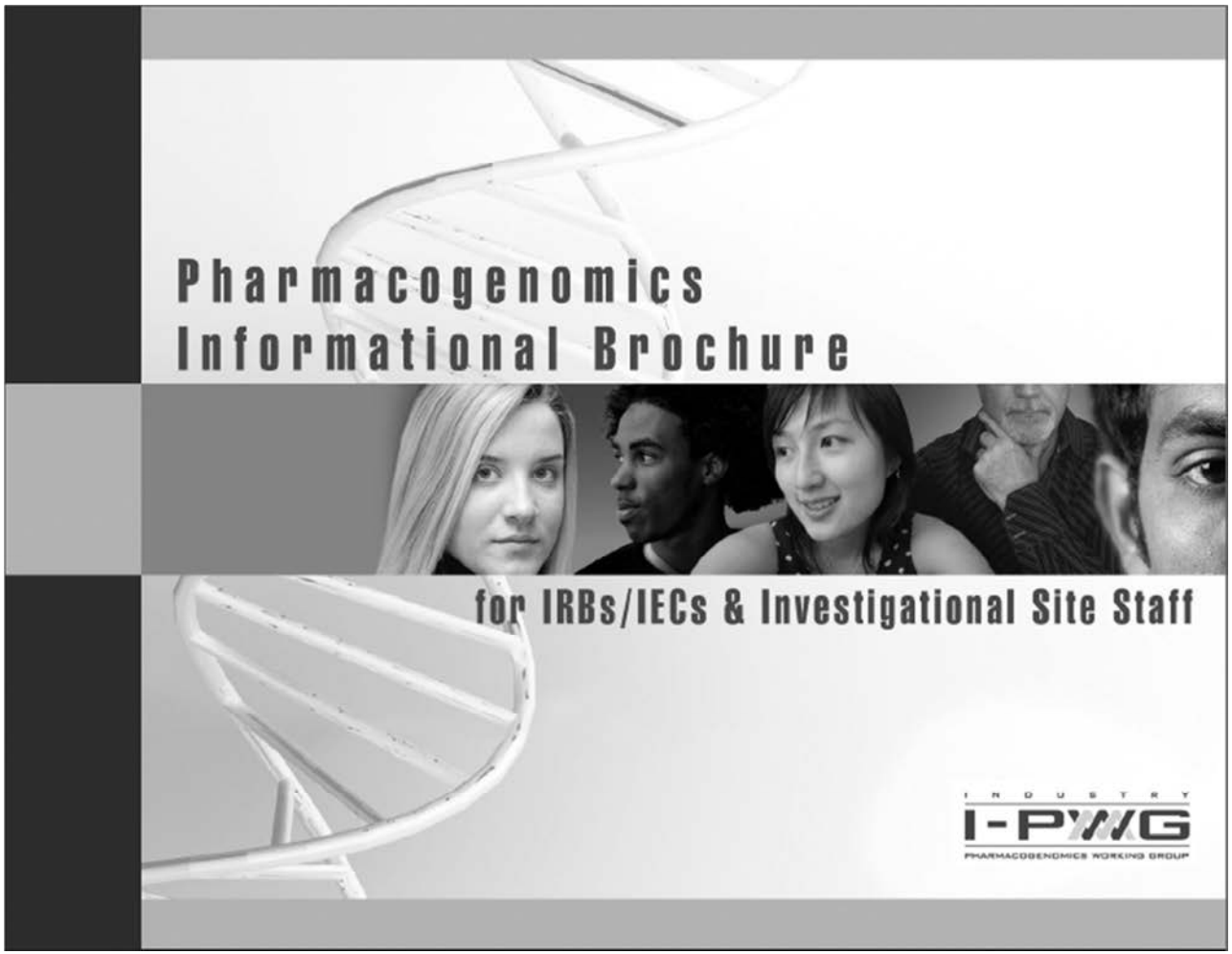
Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

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."

7.2 PHARMACOGENOMICS INFORMATIONAL BROCHURE FOR IRBS/IECS & INVESTIGATIONAL SITE STAFF



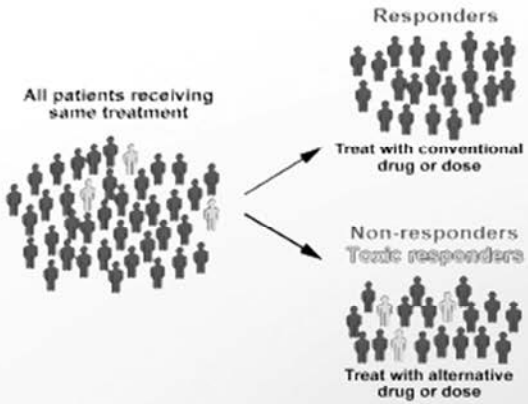
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid (DNA)**. DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

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Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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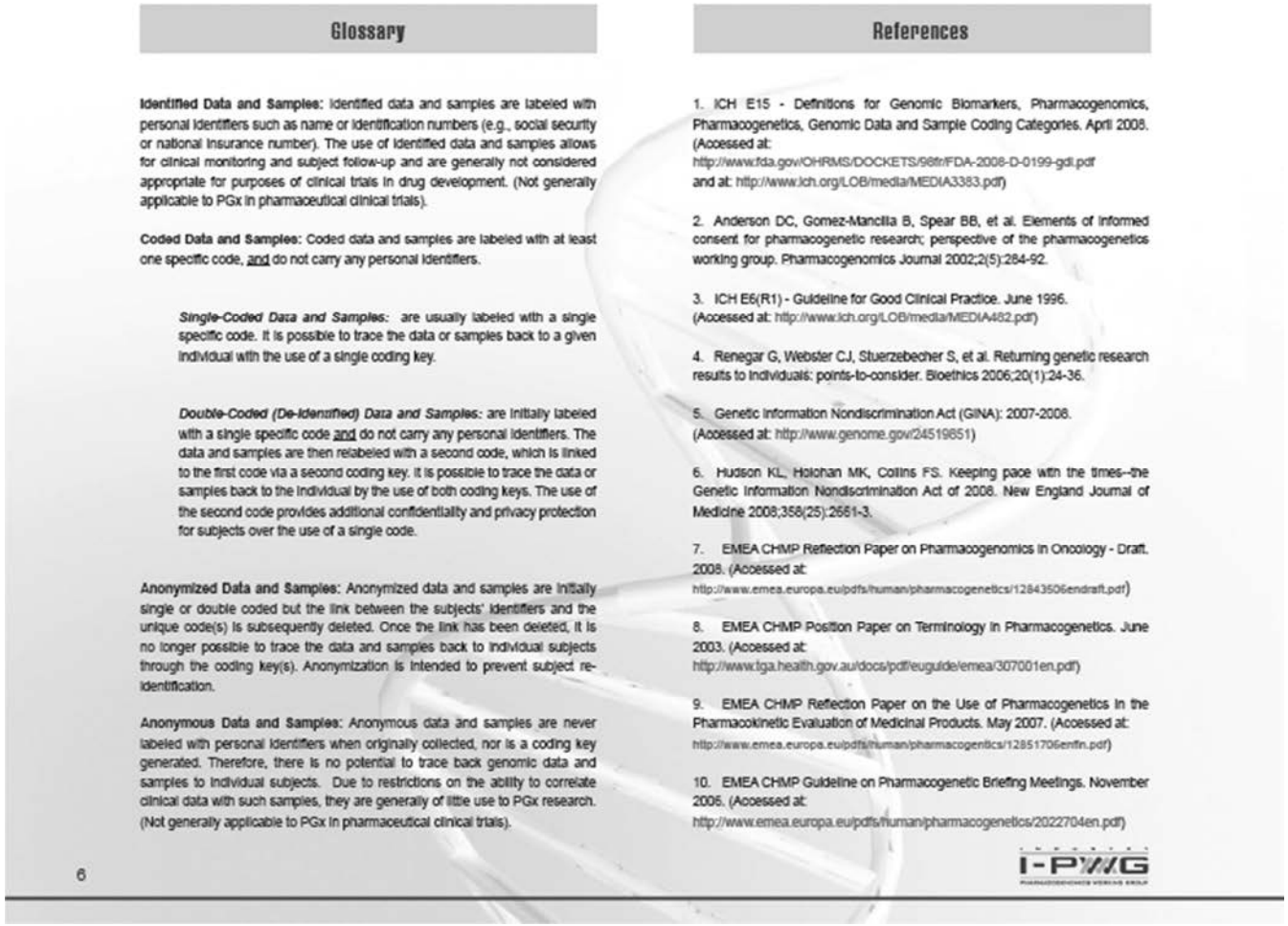

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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http://www.i-pwg.org

8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

8.2 INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any SAEs as defined in the SAFETY MEASUREMENTS section of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE