Official Protocol Title:	A Multi-Site, Open-Label, Partially-Randomized Trial of the Efficacy and Safety of Fixed Dose Elbasvir/Grazoprevir (EBR/ GZR) Based Regimens in French Subjects with Chronic Hepatitis C Virus (HCV) Genotype 4 Infection
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TITLE:

A Multi-Site, Open-Label, Partially-Randomized Trial of the Efficacy and Safety of Fixed Dose Elbasvir/Grazoprevir (EBR/GZR) Based Regimens in French Subjects with Chronic Hepatitis C Virus (HCV) Genotype 4 Infection

EudraCT NUMBER: 2016-001159-37

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.0	Trial Summary (Treatment Groups)	For Study Arm 2, the target number of treatment-naïve (TN) subjects with fibrosis stage F3-F4 in bullet #2 was changed from "0-15" to "25 (min 15)".	Due to the diminishing pool of treatment-experienced (TE) genotype (GT) 4 subjects in France, further subject enrollment will shift from TE (F0-F4) to TN (F3-F4) in order to maintain the overall enrollment target of 70 subjects in Arm 2. The new target minimum for the TN group is intended to match what is encountered in clinical practice in France. The original no minimum number for TN F3-F4 subjects was specified when the protocol was written 1.5 years ago. In the interim, expanded availability and access to direct acting antiviral (DAA) treatment in France (which prioritized treatment of patients with advanced fibrosis) has resulted in a significantly lower number of TE patients. As a result, the target enrollment minimum in Arm 2 was raised for TN subjects (F3-F4).
2.1	Trial Design	For Treatment Arm 2, the target number of TN subjects with fibrosis stage F3-F4 in the last column of Table 1 was changed from "0-15" to "25 (min 15)".	
8.1	Statistical Analysis Plan Summary	Under Study Arm 2, the target number of TN subjects with fibrosis stage F3-F4 has been changed from "0-15" to "25 (min 15)".	

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.0	Trial Summary (Treatment Groups)	For Study Arm 2, the minimum number of TE subjects with fibrosis stage F0-F4 in bullet #3 has been changed from "45 (min 30)" to "20 (min 15)" and the requirement for 10 subjects with stage F4 has been removed.	Changes to the total number of TE subjects, and specifically the removal of a minimum of TE F4 subjects, were made to account for the changing epidemiology of GT4 infections in France (i.e., the GT4 TE population in France received prioritized treatment, thereby limiting subjects who are eligible for recruitment into the current trial). The new target minimum for the TE group is intended to match what is encountered in clinical practice in France. The original minimum number of 30 TE F0-F4 subjects was specified when the protocol was written 1.5 years ago. In the interim, expanded availability and access to DAA treatment in France (which prioritized treatment of patients with advanced fibrosis) has resulted in a significantly lower number of TE patients. As a result, the target enrollment minimum in Arm 2 was lowered for TE subjects.
2.1	Trial Design	For Treatment Arm 2, the target number of TE subjects with fibrosis stage F0-F4 in the last column of Table 1 was changed from "45 (min 30)" to "20 (min 15)" and the requirement for 10 subjects with stage F4 has been removed from the table footnote.	
8.1	Statistical Analysis Plan Summary	For Study Arm 2, the minimum number of TE subjects with fibrosis stage F0-F4 has been changed from "45 (min 30)" to "20 (min 15)" and the requirement for 10 subjects with stage F4 has been removed.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
7.1.4.3	Calibration of Equipment	Removal of text referring to critical equipment.	Textual revisions were applied to clarify investigator responsibility for calibration and maintenance of trial equipment.

1.0 TRIAL SUMMARY

Abbreviated Title	EBR/GZR in TN/TE French Subjects with HCV GT4 infection
Sponsor Product Identifiers	MK-5172A (also termed MK-8742/MK-5172) elbasvir/grazoprevir (EBR/GZR)
Trial Phase	IV
Clinical Indication	Treatment of hepatitis C virus (HCV) infection
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	There are 2 treatment arms in this partially randomized study. Approximately 75 (minimum of 60) treatment-naïve (TN) subjects with stage 0-2 fibrosis will be randomized using a 2:1 ratio to Arms 1 or 2 to receive either 8 weeks or 12 weeks of EBR/GZR, respectively. TN subjects with stage 3-4 fibrosis and treatment-experienced (TE) subjects with stage 0-4 fibrosis will be assigned to Arm 2 to receive 12 weeks of EBR/GZR. The target enrollment in each group is: <u>Study Arm 1 (n=50): 8-week regimen of EBR/GZR</u> • TN subjects with fibrosis stage F0-F2 n=50 (min 40) <u>Study Arm 2 (n=70): 12-week regimen of EBR/GZR</u> • TN subjects with fibrosis stage F0-F2 n=25 (min 20) • TN subjects with fibrosis stage F3-F4 n=25 (min 15) • TE subjects with fibrosis stage F0-F4 n=20 (min 15)
Number of trial subjects	Approximately 120 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 68 weeks from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 38 or 42 weeks (depending on the treatment arm) from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 6.5 weeks, each subject will be receiving assigned treatment for approximately 8 or 12 weeks. All subjects will be followed for 24 weeks after completing study medication dosing.
Randomization Ratio	For TN subjects stage 0-2 fibrosis only: 2:1 into Arms 1 and 2 *TN subjects stage 3-4 fibrosis and all TE subjects are not randomized.*

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multi-site, open-label, partially-randomized trial of a fixed dose combination (FDC) of elbasvir (50 mg) and grazoprevir (100 mg) (EBR/GZR or MK-5172A) in subjects with chronic hepatitis C virus (HCV) genotype (GT) 4 infection to be conducted in conformance with Good Clinical Practices.

Approximately 120 subjects with chronic HCV GT4 infection, with or without advanced fibrosis, and HCV treatment-naïve (TN) or treatment-experienced (TE) as defined in Section 7.1.5.1, will be enrolled.

Approximately 75 (minimum of 60) TN subjects with stage 0-2 fibrosis (F0-F2) will be randomized using a 2:1 ratio to Arms 1 or 2, to receive either 8 weeks or 12 weeks of EBR/GZR, respectively. TN subjects with stage 3-4 fibrosis (F3-F4) and TE subjects with stage 0-4 fibrosis (F0-F4) will be assigned to Arm 2 to receive 12 weeks of EBR/GZR. The target enrollment in each treatment arm is shown in Table 1.

Table 1 Treatment Arms by Characteristics of the Target Subject Population

Arm	Study Treatment Duration	GT4 HCV Subject Characteristics		
		Previous Treatment	Fibrosis Stage	Target # of Subjects
1 (n=50)	8 weeks	TN	F0-F2	50† *(min 40)*
2 (n=70)	12 weeks	TN	F0-F2	25† *(min 20)*
		TN	F3-F4	25 *(min 15)*
		TE	F0-F4	20 *(min 15)*

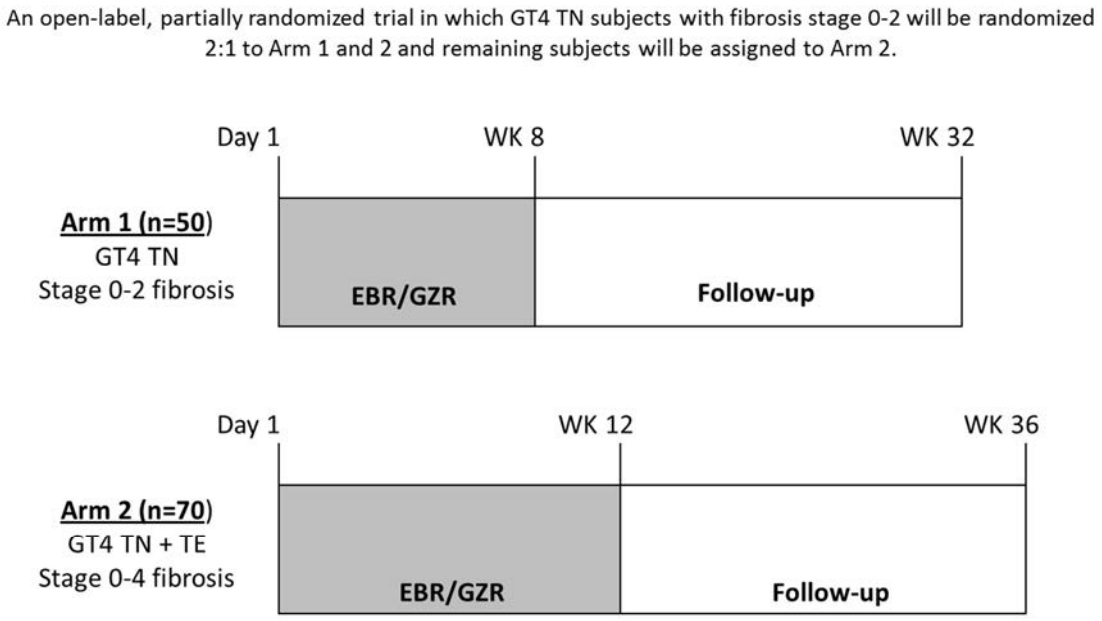
GT4 = genotype 4; HCV = hepatitis C virus; TN = treatment-naïve; TE = treatment-experienced
†: At least 60 TN F0-F2 subjects will be randomized 2:1 to Arm 1 or Arm 2.

All subjects will be followed for 24 weeks after the completion of study medication dosing. Safety and tolerability will be carefully monitored throughout the study by the Sponsor in accordance with standard procedures.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



GT4 = genotype 4; TE = treatment-experienced; TN = treatment-naïve; EBR = elbasvir; GZR = grazoprevir; WK = week.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

As this is an estimation study, there are no hypotheses.

The following objectives will be evaluated in individuals with chronic HCV GT4 infection with pre-treatment HCV RNA of at least 10,000 IU/mL.

3.1 Primary Objective(s) & Hypothesis(es)

(1) To evaluate the efficacy of each treatment arm of EBR/GZR as assessed by the proportion of subjects achieving SVR_{12} [sustained virologic response defined as HCV RNA <Lower Limit of Quantitation (LLOQ) 12 weeks after the end of all study therapy].

(2) To evaluate the safety and tolerability of EBR/GZR.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) To evaluate the efficacy of each treatment arm of EBR/GZR as assessed by the proportion of the treatment naïve F0-F2 subjects achieving SVR_{12}.

(2) To evaluate the efficacy of each treatment arm of EBR/GZR as assessed by the proportion of subjects achieving SVR_{24} (sustained virologic response defined as HCV RNA < LLOQ 24 weeks after the end of all study therapy).

(3) To evaluate resistance-associated variants (RAVs) to EBR or GZR, including the association of baseline RAVs with treatment outcomes and the emergence of RAVs in subjects who fail to achieve SVR.

3.3 Exploratory Objectives

(1) To explore the relationship between interleukin 28B (*IL28B*) genetic variation and:

- SVR_{12}
- SVR_{24}

(2) To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome may be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on EBR/GZR.

4.1.1 Pharmaceutical and Therapeutic Background

EBR: elbasvir (MK-8742) is an HCV NS5A inhibitor

GZR: grazoprevir (MK-5172) is an HCV NS3/4A protease inhibitor

EBR/GZR: elbasvir/grazoprevir (MK-5172A) is a fixed-dose combination of EBR (50 mg) and GZR (100 mg), per tablet.

4.1.1.1 Natural History of Hepatitis C Virus (HCV) Infection and Epidemiology of HCV Genotype 4 (GT4) Infection

Every year, 3 to 4 million people worldwide are newly infected with HCV [2] and approximately 80% of these will progress to chronic infection [3]. It is estimated that 130 to 170 million people, or 2% to 3% of the world's population, are chronically infected with HCV [4]. Long-term complications of chronic HCV infection develop in chronically infected individuals over the course of several years to decades. These complications include cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC) [5]. The rate of HCC development among those with chronic HCV has been estimated as 1% to 3% after 30 years [3], while over 40% of untreated individuals will develop cirrhosis within 30 years after infection [6].

HCV is genetically diverse and classified into 7 genotypes and multiple subtypes, which to date number around 70. This classification is based upon viral genome sequence homology which differs from 30% to 35% between genotypes while within each subtype there is <15% sequence variability. Some HCV genotypes, such as GT1a, 1b, 2a, and 3a are more widespread geographically, whereas others, such as GT4, have endemic foci of infection where the virus has been circulating for generations. HCV GT4 accounts for close to 20% of the 170 million HCV infections worldwide and about 85% of these infections are located in

Central Africa and the Middle East. Distribution of the remaining HCV GT4 infections mirror migration patterns from this endemic region, notably to western and southern Europe, where there are currently over 1.5 million cases [7] [8]. In France, which has an overall HCV seroprevalence of 0.6%, up to 10% of HCV infections are GT4 [4] [8]. There is considerable genetic diversity in terms of clinical isolates of GT4 that have been identified, as 17 subtypes have been confirmed to date [9]. The prevalence of these subtypes varies geographically, even within the endemic region. While GT4a predominates in Egypt, non-4a and non-4d subtypes are the most common strains isolated in Sub-Saharan Africa. Accordingly, there is a more heterogeneous distribution of GT4 subtypes in France and the rest of Europe perhaps reflecting the country of origin of the infected individual [10]. A phylogenetic analysis that combined patient derived GT4 specimens from daclatasvir late-stage clinical trials with GT4 sequences from the European HCV database demonstrated that of 128 GT4 sequences from Europe, 54 (42%) were GT4a, and 46 (36%) were GT4d, while the remaining 28 (22%) were distributed across 11 GT4 subtypes. In this same study, of 81 sequences from France, 41 (51%) were GT4a, 17 (21%) were GT4d, while the remaining 23 (28%) GT4 sequences were distributed across 8 genotype 4 subtypes [9].

4.1.1.2 General Overview of HCV Therapy and Treatment of HCV GT4 Infection

The goal of therapy for chronic HCV infection is eradication of virus, as defined by a sustained virologic response (SVR), which is tantamount to virologic cure [8]. Until recently, SVR at 24 weeks after treatment (SVR_{24}) has been considered the gold standard for treatment success as this end point is predictive of long term eradication of the virus and correlates with a reduction in symptoms and in the rate of negative clinical outcomes [11]. Specifically, SVR has been associated with improved outcomes including biochemical and histologic remission of liver disease as well as reduction in the incidence of long-term complications of HCV infection including hepatic decompensation, HCC, liver transplantation and overall mortality [12]. Given data confirming of the durability of SVR at earlier time points than SVR_{24} (such as SVR_{12}); the US FDA has concluded that SVR_{12} is suitable as a primary end point for regulatory approval [13].

Due to treatment limiting toxicities and suboptimal responses associated with interferon-based treatment, which was the standard of care up until 2011, recent drug development has focused on all-oral, interferon (IFN) free regimens comprising agents that directly and specifically inhibit viral proteins (direct-acting antivirals [DAAs]). Four DAA classes have been developed: NS3/4A protease inhibitors (PIs), NS5A inhibitors (NS5AIs), nucleotide-mimetic NS5B polymerase inhibitors (NIs), and non-nucleoside NS5B polymerase inhibitors (NNIs). Candidate medicines within each of these categories can vary substantially in terms of potency across genotypes and against resistance-associated variants (RAVs) within each genotype and sub-genotype.

There is now clear evidence that IFN-free regimens consisting of combinations of DAAs that target unique proteins integral to completion of the HCV life cycle, can be highly effective in clearing chronic HCV infection and are well tolerated. Accordingly, standard of care of treatment for chronic HCV infection is rapidly evolving to all-oral IFN-sparing DAA regimens. However, availability of DAA-based therapy may be limited in certain regions and given that the disease burden of HCV GT4 infection primarily impacts resource-constrained regions, data on the efficacy of DAA regimens in this population are limited to

pilot or single arm studies with small sample sizes. In general, DAA-based treatment responses in GT4 infection have been similar to those observed in GT1 infection; however, the impact of GT4 subtype and baseline polymorphisms on treatment response is not well characterized. A summary of published studies evaluating DAAs in GT4 is included in Table 2.

Table 2 Summary of Published Studies Evaluating DAAs in GT4

Study and Reference	Population	Regimen	SVR_{12}
NIAID SYNERGY GT4 [14] (n=21)	• 8/21 TE (prior IFN-based regimens • 7/21 compensated cirrhosis	SOF/LDV × 12 weeks	20/21 (95%) (overall) TN: 12/13 (92.3%) TE: 8/8 (100%)
PEARL-1 [15] (n=44)	• Non-cirrhotic TN	OBV/PTV/r (no RBV) × 12 weeks	40/44 (91%)
PEARL-1 [15] (n=42)	• Non-cirrhotic TN/TE	OBV/PTV/r + RBV × 12 weeks	91/91 (100%) overall TN: 42/42 (100%) TE: 49/49 (100%)
Egyptian Ancestry Trial (n=31) [16]	• TN (n=14) • TE (n =17) • Cirrhotic (n=7)	SOF + RBV × 12 weeks	21/31 (68%) TN: 11/14 (79%) TE: 10/17 (59%)
Egyptian Ancestry Trial (n=29) [16]	• TN (n=14) • TE (n=15) • Cirrhotic (n=7)	SOF + RBV × 24 weeks	27/29 (93%) TN: 14/14 (100%) TE: 13/15 (87%)
Egypt GT4 (n=52) [17]	• TN (n=25) • TE (n=21) • Cirrhotic (n=8)	SOF + RBV × 12 weeks	40/52 (77%) TN: 21/25 (84%) TE: 19/27 (70%) Cirrhotic: 5/8 (63%)
Egypt GT4 (n=51) [17]	• TN (n=24) • TE (n=27) • Cirrhotic (n=9)	SOF + RBV × 24 weeks	46/51 (90%) TN: 22/24 (92%) TE: 24/27 (89%) Cirrhotic: 7/9 (78%)
NEUTRINO (n=28) [18]	• TN only • Cirrhotic and non-cirrhotic	Peg-IFN + RBV + SOF × 12 weeks	27/28 (96%)
Study 1119: France Open Label GT4 (n=44) and 5 Study [19]	• TN (n=22) • TE (n=22) • Cirrhotic (n=10)	SOF/LDV × 12 weeks	41/44 (93%) TN: 21/22 (96%) TE: 20/22 (91%)
ION-4 (n=8) [20]	• TN/TE • HIV co-infected • Cirrhotic and non-cirrhotic	SOF/LDV × 12 weeks	8/8 (100%)

Study and Reference	Population	Regimen	SVR_{12}
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/SIM × 12 weeks	8/8 (100%)
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/SIM × 24 weeks	10/11 (91%)
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/SIM/RBV × 12 weeks	1/1 (100%)
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/SIM/RBV × 24 weeks	6/6 (100%)
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/DCV × 12 weeks	16/18 (89%)
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/DCV × 24 weeks	4/4 (100%)
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/DCV/RBV × 12 weeks	3/3 (100%)
French Observational Cohort: ANRS CO22 HEPATHER [21] (prelim results)	• TN • TE • Cirrhosis: > 80% for all arms evaluated	SOF/DCV/RBV × 24 weeks	6/6 (100%)

DAA = direct-acting antiviral; DCV = daclatasvir; GT = genotype; HIV = human immunodeficiency; LDV = ledipasvir; OBV = ombitasvir; PTR/r = paritaprevir/ritonavir; SOF = sofosbuvir; SIM=simeprevir; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naïve.

4.1.1.3 EBR/GZR in HCV Genotype 4 Infection

The efficacy of the GZR 100 mg and EBR 50 mg with and without (±) RBV in GT4 infected subjects was evaluated in an integrated analysis of the phase 2/3 clinical program [1]. Two pooled datasets were analyzed: (1) treatment-naïve (TN) subjects who received 12 weeks of EBR/GZR ± RBV; and (2) treatment-experienced (TE) subjects, defined as those who had previously failed pegylated interferon (peg-IFN) + RBV (PR) who received 12, 16, or 18 weeks of GZR/EBR ± RBV. A total of 103 GT4-infected subjects were evaluated including 66 subjects who were treatment-naïve and 27 subjects who were treatment-experienced. Results from this analysis are summarized in Table 3.

Table 3 Results from Integrated Analysis of EBR/GZR Efficacy in GT4 [1]

GT4 Subgroup	Regimen	Duration (weeks)	SVR_{12} n/N (%) [CI] FAS[1]	Non-SVR Reason
Treatment-naïve Subjects				
TN	EBR/GZR ± RBV	12	64/66 (97%) [89.4-99.6]	
TN	EBR+GZR	12	54/56 (96%)	1 - Relapse 1 - Other[2]
TN	EBR+GZR + RBV	12	10/10 (100%)	
TN with cirrhosis	EBR/GZR	12	6/6 (100%)	
Treatment-experienced Subjects				
TE	EBR+GZR ± RBV	12-18	32/37 (86.5%) [71.2-95.4]	
TE	EBR+GZR	12	7/9 (77.8%)	1 - Relapse 1 - Discontinuation due to AE
TE with cirrhosis	EBR+GZR	12	4/6 (67%)	1 - Relapse 1 - Discontinuation due to AE
TE	EBR+GZR+RBV	12	14/15 (93.3%)	1 - Relapse
TE with cirrhosis	EBR+GZR+RBV	12	4/5 (80%)	1 - Relapse
TE	EBR+GZR	16-18	3/5 (60%)	1 - Rebound 1 - Breakthrough
TE with cirrhosis	EBR+GZR	16-18	1/2 (50%)	1 - Rebound
TE	EBR+GZR+RBV	16-18	8/8 (100%)	
TE with cirrhosis	EBR+GZR+RBV	16-18	4/4 (100%)	

AE = adverse event; CI = confidence interval; EBR = elbasvir; FAS = full analysis set; GZR = grazoprevir; OTF = on treatment virologic failure; RBV = ribavirin; TE = treatment-experienced; TN = treatment naive.

[1] FAS: analysis includes all subjects who received at least one dose of study drug.
[2] "Other" includes subjects who did not achieve SVR but did not meet virologic failure criteria (e.g., lost to follow-up, withdrew consent), nor discontinued due to an AE.

4.1.1.4 Current French Treatment Guidelines for HCV GT4

The June 2015 French national treatment guidelines [22] provide guidance on management of HCV GT4 infection based on the level of available evidence supporting each recommended regimen. These guidelines, summarized in Table 4, include recommendations for regimens that as of June 2015, were either available or in late stage development.

Table 4 Summary of French National Treatment Guidelines

Population	Regimen (Available in June 2015)	Duration	Level of Evidence
Non-cirrhotic TN/TE			
	SOF+SIM	12 weeks	C
	SOF+DCV	12 weeks	C
	SOF+LDV	12 weeks	B
	OBV/PTV/r + RBV	12 weeks	A
Compensated Cirrhotic TE/TN			
	SOF+SIM+RBV	12 weeks	C
	SOF+SIM	24 weeks	C
	SOF+DCV+RBV	12 weeks	C
	SOF+DCV	24 weeks	C
	SOF+LDV+RBV	12 weeks	EA
Non-cirrhotic TN: Late Stage Development Regimen			
	EBR/GZR	12 weeks	C
	SOF/GS-5816	12 weeks	C
A = established scientific evidence; B = scientific assumption; C = low level of evidence; DCV = daclatasvir; EA = expert agreement; LDV = ledipasvir; OBV = ombitasvir; PTR/ r= paritaprevir/ritonavir; SIM=simeprevir; SOF = sofosbuvir; TE=treatment-experienced; TN=treatment-naïve.			

4.1.2 Background of Elbasvir/Grazoprevir

Please refer to the EBR and GZR Investigator Brochures (IBs) for more information on the pre-clinical and clinical studies with EBR/GZR.

4.1.3 Ongoing Clinical Trials

Please refer to the respective IBs for details regarding the preliminary results of ongoing clinical studies.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Optimal management of HCV GT4 infection is not well defined as current treatment guidelines in France are based on efficacy data from smaller studies. Although regimens recommended in these guidelines offer improved safety and efficacy over peg-IFN based therapy, evaluation and availability of newer DAAs such as EBR/GZR may expand treatment options for those not optimally managed with currently available therapies.

4.2.1.1 Rationale for Study Population (GT4 Infection)

The prevalence of HCV GT4 infection is 10% in France and increasing across all of western and southern Europe. With over 30 million cases worldwide, GT4 infection contributes significantly to the disease burden attributable to chronic HCV infection. Evaluation of strategies aimed at optimizing management of GT4 infection, such as treatment with shorter RBV-free regimens may eventually lead to expanded access to treatment in the resource limited settings where GT4 infection is endemic.

4.2.1.2 Rationale for Study Population (F0-F2 Fibrosis, TN, and TE subjects)

Although current French National HCV Treatment Guidelines imply that therapy should be proposed for almost all patients with HCV infection, including cirrhotic, non-cirrhotic, TN, and TE patients, consideration of eligible candidate's accounts for practical limitations to treatment access, including budgetary constraints. Accordingly, treatment recommendations outlined in these guidelines entail prioritizing treatment in those TN and TE patients with stage 2 or higher fibrosis, i.e., those who are at higher risk of developing complications from liver disease if untreated. However, the guideline authors do point out that universal access to HCV treatment for all patients in France is a goal by 2025 and that gradual extension of treatment indications will be considered by health authorities [22]. All currently recommended regimens for HCV GT4 patients are at least 12 weeks in duration and as seen in Table 4, the regimen with the most supporting evidence (ombitasvir [OBV]/PTV/r + RBV × 12 weeks) includes RBV. Thus evaluation of whether a shorter 8-week RBV-free regimen is a viable option in subjects with F0-F2 fibrosis is important as treatment expansion strategies aimed at the goal of universal access are developed. Furthermore, this trial proposes to evaluate 2 unique treatment arms, thus inclusion of a broad spectrum of GT4 subjects can aid in understanding the merits of these regimens relative to specific patient subgroups.

4.2.1.3 Rationale for Study Population (SOF + RBV and SOF + peg-IFN/RBV failures)

TE subjects who have failed SOF with or without RBV are eligible for this **study as it is highly unlikely they will respond any differently to EBR/GZR than other** IFN/RBV failures. Given that SOF utilizes a mechanism of action distinct from either EBR or GZR, RAVs selected by SOF maintain full susceptibility to EBR and GZR. Furthermore, to date, identification of SOF RAVs in GT4 subjects failing either SOF/RBV or SOF/peg-IFN/RBV is exceedingly rare. Of the 17 patients who did not achieve a SVR_{12} in the Egyptian GT4 study [17] and the one failure in the NEUTRINO study [18], none had the signature RAV for SOF, the S282T, suggesting that GT4 subjects who fail these SOF/RBV +/-peg-IFN will have future treatment options in the unlikely event they fail EBR/GZR. The rationale for excluding all other DAA-based failures is that treatment with any DAA-including regimen other than SOF + RBV or SOF + peg-IFN would have included either an NS5A or NS3 inhibitor, thus those who failed these regimens are at increased risk for baseline resistance to either EBR and/or GZR.

4.2.1.4 Rationale for Study Population (Compensated Cirrhotic Patients)

Compensated cirrhotic patients are included given that they are at the highest risk of developing complications from liver disease [23] and are considered to be a high priority for treatment in the French guidelines. SVR confers numerous clinical benefits including improvement in mortality, reduction in HCC and reduction in hepatic decompensation [12], hence the need to treat those who are at the greatest risk for developing these outcomes. Current treatment recommendations for GT4 cirrhotic patients (Table 4) include either 24-week regimens or 12-week regimens that include RBV. There are no 12-week RBV free regimens included in the current French treatment guidelines for cirrhotic GT4 patients and this study proposes to evaluate such a regimen in both TE and TN cirrhotic patients. In addition to increasing pill burden, RBV is associated with toxicities such as anemia, its use typically requires additional monitoring, and administration may not be optimal in the setting of significant comorbidities such as cardiac and renal disease. An integrated analysis of 402 compensated cirrhotic patients with HCV GT1, GT4, or GT6 infection treated with EBR and GZR ± RBV for 12 to 18 weeks demonstrated comparable efficacy to what is seen in non-cirrhotic subjects. A small number of GT4 subjects were included in this analysis and as seen in Table 3, 6/6 TN GT4 cirrhotics and 4/5 TE GT4 cirrhotics achieved SVR_{12}. The overall efficacy of all compensated cirrhotic GT1, GT4 and GT6 (SVR_{12}) TN and TE subjects treated with 12 weeks of EBR/GZR was 98% (135/138) and 89% (48/54), respectively. Among TE cirrhotics, 2 of the 6 subjects failed to attain a SVR due to administrative reasons [24]. These data support inclusion of compensated cirrhotic subjects in the proposed study Arm 2.

4.2.1.5 Rationale for Study Population (HIV Co-infection)

Subjects co-infected with human immunodeficiency virus (HIV) will not be excluded from this trial given that treatment outcomes with DAA-based regimens are no different in HCV mono-infected versus co-infected HCV/HIV patients with preserved immune function [20]. Similar conclusions have been observed in the EBR/GZR clinical program, wherein, HIV co-infected GT1- and GT4-infected subjects had similar high efficacy following EBR/GZR therapy in Phase 3 studies [25]. In the EBR/GZR Phase 3 program, Protocol PN061 treated GT1-, GT4-, and GT6-infected subjects co-infected with HIV with and without cirrhosis [26]. All were treated with a regimen of EBR/GZR without RBV for 12 weeks and the efficacy was 96% (210/218) and was 100% in the 16% of co-infected subjects with cirrhosis. The subject response rate across all demographics, including Black subjects, was similar to the mono-infected subjects. With similar efficacy achieved with EBR/GZR in mono- and co-infected subjects, this trial will co-enroll HIV infected subjects in all treatment arms.

4.2.1.6 Rationale for Sample Size

The sample size for each treatment group in this study (n = 50 in Arm 1 and n = 70 in Arm 2) was selected based on the knowledge of the epidemiology of HCV infection in France. This is an exploratory study with no formal hypotheses thus the sample size is reflective of the number of subjects that are likely to be enrolled in each treatment arm. The current sample size will be used to estimate efficacy and safety of these 2 treatment regimens (refer to Table 17 and Table 18 in Section 8.9).

4.2.2 Rationale for Dose Selection/Regimen/Modification

Dose Selection for EBR

An EBR dose of 50 mg daily (QD) was selected based on a Phase 1b monotherapy study in HCV-infected subjects, EBR PN002, and a Phase 2a dose-ranging study (PN035 Part A), as well as the favorable efficacy and safety profile demonstrated in a large Phase 2/3 program in which approximately 2000 subjects were treated with a dose of EBR (50 mg) including subjects with cirrhosis, HIV co-infection, and prior treatment experience. For detailed information, please refer to the IB.

Dose Selection for GZR

A GZR dose of 100 mg QD was selected based on Phase 2 dose-ranging studies (PN003, PN038) as well as the favorable efficacy and safety profile demonstrated in a large Phase 2/3 program in which approximately 2000 subjects were treated with a dose of GZR (100 mg) including subjects with cirrhosis, HIV co-infection and prior treatment experience. For detailed information, please refer to the IB.

4.2.2.1 Rationale for 8-week Regimen of EBR/GZR in TN GT4 Subjects with F0-F2 Fibrosis (Arm 1)

Preclinical studies demonstrate that the in vitro activity of both EBR and GZR against GT4 is similar to GT1b when assessed in HCV replicon cell-based assays. This work included evaluation of most of the common GT4 subtypes that are associated with clinical disease. For reference, available EBR and GZR in vitro susceptibility data for all GT4 subtypes that were identified from French patients in the study discussed in Section 4.1.1.1 [9] are summarized in Table 5 and Table 6 with GT1b EC50 provided for comparison.

Table 5 EBR and GZR *In Vitro* Susceptibility Data for All GT4 Subtypes Identified from French Patients

GT4 Subtype	Frequency of GT4 subtype among 81 isolates from France sequenced in ref [9] n (%)	Number of GT4 subtype replicons assayed	Range of GZR EC_{50} (nM)	GZR EC_{50} for GT1b in Con 1 replicon for reference (nM ± SD)
4a	41 (50.6%)	1	0.3	0.5 ± 0.3
4d	17 (21%)	1	0.6	0.5 ± 0.3
4f	10 (12.3 %)	0	n/a	0.5 ± 0.3
4k	3 (3.7%)	0	n/a	0.5 ± 0.3
4g	2 (2.5%)	2	0.15-0.33	0.5 ±-0.3
4c	2 (2.5%)	0	n/a	0.5 ±-0.3
4q	2 (2.5%)	0	n/a	0.5 ±-0.3
4t	2 (2.5%)	0	n/a	0.5 ±-0.3
4n	1 (1.2%)	0	n/a	0.5 ±-0.3
4p	1 (1.2%)	0	n/a	0.5 ±-0.3

Table 6 EBR and GZR *In Vitro* Susceptibility Data for All GT4 Subtypes Among 81 Isolates Identified from French Patients

GT Subtype	Frequency of GT Subtype among 81 isolates from France sequenced in ref [9] n (%)	Number of GT4 subtype replicons assayed	Range of EBR EC_{50} nM	GZR EC_{50} for GT1b in Con 1 replicon for reference (nM ± SD)
4a	41 (50.6%)	3	.0002-.003	.003 ± .001
4d	17 (21%)	2	.0004-.0005	.003 ± .001
4f	10 (12.3 %)	1	.0019	.003 ± .001
4k	3 (3.7%)	0	n/a	.003 ± .001
4g	2 (2.5%)	2	.072-.0006	.003 ± .001
4c	2 (2.5%)	0	n/a	.003 ± .001
4q	2 (2.5%)	1	.0005	.003 ± .001
4t	2 (2.5%)	0	n/a	.003 ± .001
4n	1 (1.2%)	0	n/a	.003 ± .001
4p	1 (1.2%)	0	n/a	.003 ± .001

The activity of both EBR and GZR against GT4a and 4d, which appear to be the most prevalent subtypes in France, is comparable to what is seen against GT1b. This similar potency *in vitro* does appear to correlate with *in vivo* efficacy. As demonstrated in Table 7, the treatment response rate of 12 weeks of EBR/GZR in the pooled TN GT4 dataset [10] was similar to the response rate in the in the TN GT1b patients treated in PN035, a randomized, placebo-controlled study that included both cirrhotic and noncirrhotic subjects with HCV GT1, 4, and 6 infection [27].

Table 7 Treatment Response Rates After 12 Weeks of EBR/GZR in Treatment-Naïve Subjects

Regimen	Duration	SVR_{12} GT1b (PN035)	SVR_{12} GT4 (pooled analysis)
EBR/GZR	12 weeks	129/131 (99%)	54/56 (96%)

The comparable *in vitro* and clinical profiles of EBR and GZR in GT4 and GT1b infection suggest that efficacy of regimens not yet studied in TN GT4 patients may be similar to what was seen in GT1b infection. Accordingly, justification for the 8-week regimen proposed for TN GT4 subjects with F0-F2 fibrosis is based on the high efficacy observed when this same regimen was given to a similar GT1b population. In PN035, one of the treatment arms included an 8-week regimen of EBR and GZR in noncirrhotic TN subjects with GT1b infection and demonstrated that 28/29 TN GT1b subjects with F0-F2 fibrosis achieved SVR_{12}.

4.2.2.2 Rationale for 12-week Regimen of EBR/GZR in TN GT4 (F3-F4)

As seen in Table 3, the efficacy of EBR/GZR was over 96% when given for 12 weeks in TN GT4 subjects enrolled in the phase 2/3 clinical program and there was no difference in TN GT4 subjects with cirrhosis compared to those without cirrhosis supporting continued evaluation of this regimen for GT4 infected subjects in France.

4.2.2.3 Rationale for 12-week Regimen of EBR/GZR in TE GT4 (F0-F4)

As discussed previously, EBR and GZR have comparable in vitro activity against GT4 and GT1b replicons and parallels in treatment response were noted between TN GT4 and GT1b subjects treated with 12 weeks of EBR/GZR. As seen in Table 8, in the pooled Phase 2/3 dataset, TE GT1b subjects responded well to 12 weeks of EBR and GZR while the response rates were lower in a much smaller sample size of TE GT4 subjects. Among the 2 TE GT4 subjects who did not achieve SVR12, one subject relapsed and a second discontinued due to an adverse event (AE) that was not drug related. Similar treatment responses to those observed in TE GT1b infection are expected in TE GT4 subjects and the difference noted above may be modulated by the small sample size of TE GT4 subjects making it difficult to assess the validity of this result. Accordingly, additional work to optimize management of TE GT4 infection, specifically by studying a 12-week RBV free regimen, is warranted.

Table 8 Treatment Response Rates after 12 Weeks of EBR/GZR in Treatment-Experienced Subjects

Regimen	Duration	SVR_{12} GT1b	SVR_{12} GT4
EBR/GZR	12 weeks	54/56 (96%)	7/9 (78%)

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary measurement for efficacy in this study is the plasma HCV RNA level. Long term suppression of HCV RNA, typically reported as sustained virologic response (SVR), has been associated with improved outcomes in patients with chronic hepatitis C infection as measured by biochemical and histological remission of liver disease. Most available data suggest that SVR following antiviral therapy reduces the risk of progression to cirrhosis and may prevent the development of severe liver complications and improve survival [28].

The primary evaluation of efficacy in this trial is based on SVR_{12} (sustained virologic response 12 weeks after the end of all study therapy), the current standard ever since first used for registration of simeprevir and sofosbuvir. Because there is a high degree of concordance between SVR_{12} and SVR_{24} [29], SVR_{12} is used as the primary endpoint for registration of DAAs [13].

Other secondary evaluations of efficacy are based on SVR_{24} (sustained virologic response 24 weeks after the end of all study therapy).

Detailed definitions for evaluation for SVR are provided later in this section.

4.2.3.1.1 Measurement of HCV RNA

HCV RNA levels in plasma will be measured on blood samples drawn from each subject at various time points prior to, during, and after dosing, as indicated in the Trial Flow Chart (Section 6.0). Samples are collected and processed as per instructions provided by the central laboratory manual (assay type indicated in central laboratory manual).

Results from the sample collected at the screening visit are used to determine eligibility. Samples collected at other time points are used for efficacy analyses. They are also used to identify subjects who meet virologic failure criteria.

The nomenclature detailed in Table 9 will be used when describing HCV RNA levels:

Table 9 Nomenclature for Describing HCV RNA Levels

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

4.2.3.1.1.1 Definition of Efficacy Endpoints

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

- 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.

4.2.3.1.1.2 Definition of Virologic Failure: Non-Response, Rebound, Virologic Breakthrough and Relapse

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

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

4.2.3.1.2 Viral Resistance Measurements

HCV resistance measurements

Resistance-associated variants (RAVs) of the hepatitis C virus can lead to increased risk of failure to DAA therapy. In addition, subjects with virologic failure may develop RAVs.

Blood samples for viral resistance assays are collected on all subjects at Baseline (Day 1) to determine the impact of baseline RAVs on response to EBR and GZR.

To better understand the presence of RAVs after treatment with a regimen containing EBR/GZR, samples will be collected at virologic failure confirmation visits and all follow-up visits after virologic failure is confirmed. Samples will be tested for any subject meeting virologic failure criterion who has detectable virus >1000 IU/mL. These same subjects who meet any virologic failure criterion will have samples collected at all subsequent follow-up visits to be assessed for RAVs, if the virus is detectable and >1000 IU/mL.

Subjects who fail due to early discontinuation of study medication and continue in the trial will also have samples collected and tested for RAVs at each follow-up visit, if the virus is detectable and >1000 IU/mL.

Analysis of RAVs will entail a variety of techniques that may include population sequencing and/or next generation sequencing. Additionally, genotypic and investigational assays may be employed to differentiate virologic failure from re-infection. Resistance testing may also be performed on leftover HCV RNA plasma samples.

4.2.3.2 Safety Endpoints

The safety and tolerability of the study regimens will be assessed by a clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examinations, and standard laboratory safety tests at appropriate time points as specified in the Trial Flow Chart (Section 6.0). Adverse events are graded and recorded according to Section 7.2. Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

4.2.3.3 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

In addition to studying variation across the human genome, for example, *IL28B* genetic variants will specifically be investigated for understanding variation in clinical endpoints for example, but not limited to, SVR and other efficacy and safety measurements.

4.2.3.4 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

Elbasvir/Grazoprevir

In Phase 1-3 studies, 1234 healthy volunteers, 66 non-HCV-infected persons with liver or kidney impairment, and 2704 HCV-infected subjects have been treated with any dose or regimen of EBR and/or GZR, with or without RBV. At a dose of EBR (50 mg) and GZR (100mg) in ~ 2000 subjects, high efficacy and a favorable safety profile has been demonstrated including subjects with cirrhosis, HIV co-infection, chronic kidney disease and history of prior HCV treatment failure.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with chronic HCV GT4 infection who are at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. be ≥ 18 years of age on day of signing informed consent
2. be a current resident of France
3. have HCV RNA (≥ 10,000 IU/mL in peripheral blood) at the time of screening
4. have documented chronic HCV GT4 (with no evidence of non-typeable or mixed genotype) infection and meet the definition below:
    a. positive for anti-HCV antibody, HCV RNA, or HCV GT4 at least 6 months before screening, **or**
    b. positive for anti-HCV antibody or HCV RNA at screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed before enrollment with evidence of CHC disease, such as the presence of fibrosis)
5. have one of the below liver staging assessments as follows:
    a. Liver biopsy performed within 24 months of Day 1 of this study (if subject has cirrhosis, there is no time restriction on biopsy)

b. FibroScan® performed within 12 months of Day 1 of this study with interpretable result in kilopascals (kPa) as follows

- Fibrosis score of F0-F2 = <8.0 kPa
- Fibrosis score of F3 = 8.0 – 12.5 kPa
- Cirrhosis (F4) = >12.5 kPa

c. For cirrhotic (F4) subjects only: A FibroTest® (FibroSure®)* performed during Screening with a score of >0.75 **and** an aspartate aminotransferase (AST): platelet ratio index (APRI) of >2.

APRI formula: AST÷lab upper limit of normal (ULN) for AST x 100÷ (platelet count÷100) (APRI calculation to be provided by the central laboratory).

*If FibroTest®/APRI results are not available or if the FibroTest®/APRI score is indeterminant then either a liver biopsy or interpretable FibroScan® result, performed within timeframe above, must be obtained and reported for study entry and liver fibrosis staging.

NOTE: In cases where more than one liver fibrosis staging assessment is available, only one result may be used to determine fibrosis status.

6. have a prior treatment history of either of the following (see Section 7.1.5 for definitions):
   a. HCV treatment-naïve (TN)
   b. HCV treatment-experienced (TE) with IFN +/- RBV +/- SOF:
      - On-treatment Failure
      - Relapser
      - Other/intolerant

      NOTE: When available, documentation of prior IFN +/- RBV +/- SOF treatment history should include clinic notes or referral letter documenting regimen administered, approximate dates of treatment, approximate date of virologic failure, and a history of laboratory confirmed prior virologic failure or documented intolerance to allow for categorization of prior regimen. If the subject was treated with a regimen more than once, the categorization must be based on the most recent round of treatment.
7. meet one of the following categories:
   a. the subject is a male.
   b. the subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

c. the subject is a female who is of reproductive potential and agrees to avoid becoming pregnant from Day 1 through 14 days after the last dose of study drug or longer if dictated by local regulations by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

8. understands the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.
9. provides written informed consent for the trial. The subject may also provide consent for future biomedical research (FBR). However, the subject may participate in the main trial without participating in FBR.

For HIV co-infected subjects, these additional criteria must also be met:

10. have HIV-1 infection documented at any time prior to screening by any licensed rapid HIV test or HIV enzyme or chemiluminescense immunoassay (E/CIA) test kit and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA viral load.

11. meet one of the following criteria:
    a. If not currently on antiretroviral therapy (ART) and has no plan to initiate ART treatment while participating in this study:
        i. Subjects not on ART must have CD4+ T-cell count > 500 cells/mm^3 at screening.
    b. have well controlled HIV on ART, defined as:
        i. must have achieved and maintained virologic suppression (defined as confirmed HIV RNA level below the LLOQ of available assay) on HIV ART at least 8 weeks prior to study entry (Day 1).
            a) ART regimen must contain only the following antiretroviral medications: tenofovir, abacavir, lamivudine, emtricitabine, raltegravir, dolutegravir, and rilpivirine.
            b) Dose modifications or changes in drugs during the 4 weeks prior to study entry (Day 1) are not permitted.
        ii. have HIV RNA < LLOQ at screening
        iii. subjects on ART must have a CD4+ T-cell count > 200 cells/mm^3 at screening.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. is under the age of legal consent, is mentally or legally incapacitated, has significant emotional problems at the time of pre-study screening visit or expected during the conduct of the study or has a history of a clinically significant psychiatric disorder which, in the opinion of the investigator, would interfere with the study procedures.
2. had prior treatment (defined as 1 dose or more) with DAA therapy not listed in **Section 7.1.5.1**.
3. has evidence of decompensated liver disease manifested by the presence of or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs or symptoms of active advanced liver disease.
4. is classified as Child-Pugh B or C or has a Child Pugh-Turcotte score (CPT) > 6:

   NOTE: To calculate the Child-Pugh score, refer to the following website: http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality
5. has cirrhosis and liver imaging within 6 months of Day 1 showing evidence of hepatocellular carcinoma (HCC) or is under evaluation for HCC.

   NOTE: If liver imaging within 6 months of Day 1 not available, imaging is required during screening.

6. is hepatitis B surface antigen [HBsAg] positive at screening.

   NOTE: Subjects who are HBsAg negative at screening, but who are hepatitis B core antibody (anti-HBc) positive at screening may be included. For all anti-HBc positive subjects, hepatitis B virus (HBV) deoxyribonucleic acid (DNA) will be assessed at screening, and both HBV DNA and HBsAg will be monitored during the trial. Additional details can be found in Section 7.1.3.4 – HBV Evaluation and Section 7.2.3.2 – Events of Clinical Interest.

7. is under evaluation for active or suspected malignancy, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer.
8. is taking or plans to take any of the prohibited medications listed in S**ection 5.5**.
9. is currently participating or has participated in a study with an investigational compound within 30 days of signing informed consent and is not willing to refrain from participating in another such study during the course of this study.
10. has clinically-relevant drug or alcohol abuse within 12 months of screening, in the opinion of the investigator that would compromise the patient's ability to participate in the trial.
11. is a female and is pregnant or breastfeeding, or expecting to conceive or donate eggs from Day 1 through 14 days after the last dose of study drug or longer if dictated by local regulations, OR a male subject who is expecting to donate sperm from Day 1 through 14 days after the last dose of study drug or longer if dictated by local regulations.
12. has any clinically-significant illness (other than HCV) or any other major medical disorder that in the opinion of the investigator may interfere with subject treatment, assessment or compliance with the protocol or any medical/surgical conditions that may result in a need for hospitalization during the period of the study; subjects currently under evaluation for a potentially clinically-significant illness (other than HCV) are also excluded.

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

13. has exclusionary laboratory values at the screening visit as listed in Table 10

    NOTE: If any of the laboratory exclusion criteria in Table 10 are met, the site may have the abnormal value retested once. No other tests may be repeated for determining study entry eligibility.

Table 10 Laboratory Exclusion Criteria

Laboratory Assessment	Exclusionary Parameters
Hemoglobin	< 10 g/dL in females or < 11 g/dL in males
Platelets	$< 40 \times 10^3/\mu L$
Serum Albumin	< 3.0 g/dL
INR	> 1.7 (unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR)
ALT	> 10 × ULN
AST	> 10 × ULN

14. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 11.

Table 11 Trial Treatment

Drug	Weight	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-5172A (fixed dose combination of EBR/GZR)	NA	50 mg/ 100 mg	QD	Oral	Arm 1: 8 weeks Arm 2: 12 weeks	Experimental

The first dose of trial treatment will be administered at the trial site at Visit 2 (Day 1). All other dosing will be performed by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose of EBR/GZR to each subject.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Dose modification of EBR/GZR is not permitted.

5.2.2 Timing of Dose Administration

EBR/GZR

Subjects will be instructed to take EBR/GZR without regard to food.

If a subject misses a dose of EBR/GZR and it is less than 8 hours before the next dose, the missed dose should be skipped and the normal dosing schedule resumed. Subjects should not double the next dose in order to compensate for what has been missed.

If for any reason EBR/GZR needs to be interrupted, it can be interrupted for up to 3 consecutive days. If the interruption lasts for more than 3 consecutive days, consult the Sponsor Protocol team.

5.2.3 Trial Blinding

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

5.3 Randomization or Treatment Allocation

In this open-label, partially randomized study, approximately 120 subjects will be enrolled. Approximately 75 (minimum of 60) TN subjects with stage 0-2 fibrosis will be randomized 2:1 to Arms 1 and 2, respectively. A total of approximately 45 TN subjects with stage 3-4 fibrosis and TE subjects with stage 0-4 fibrosis will be assigned (not randomized) to Arm 2. The treatment allocation (Table 1) will be implemented centrally using an interactive voice response system/integrated web response system (IVRS/IWRS).

5.4 Stratification

The randomized subjects will be stratified by baseline HCV RNA viral load: less than or equal to 800,000 IU/mL and greater than 800,000 IU/mL.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

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

- At each visit, subjects should be questioned about any new drug they are taking
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.

- Drugs known to be hepatotoxic (i.e., drugs with a warning of hepatotoxicity in the package insert) should be avoided during the dosing period. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nij.gov website.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the trial.

The following medications/therapies are prohibited during the dosing period and for 14 days before and after the dosing period:

Known hepatotoxic drugs, including but not limited to:

- Etifoxine
- Isoniazid
- Nitrofurantoin
- Phenytoin
- Oral Ketoconazole

Strong and moderate CYP3A/P-gp inducers, including but not limited to:

- antibiotics: nafcillin
- antimycobacterials: rifampin
- anticonvulsants: carbamazepine, phenytoin
- endothelin Antagonists: bosentan
- Herbal Products: St. John's wort
- HIV Medications: efavirenz, etravirine
- Wakefulness-Promoting Agents: modafinil

OATP inhibitors, including but not limited to:

- immunosuppressants: cyclosporine
- antimycobacterials: rifampin
- HIV Medications: atazanavir, darunavir, lopinavir, saquinavir, tipranavir

HIV medications:

- Cobicistat-containing regimens - elvitegravir/ cobicistat/emtricitabine/ tenofovir (disoproxil fumarate or alafenamide)
- atazanavir,
- darunavir
- lopinavir
- saquinavir

- tipranavir
- efavirenz
- etravirine

HMG-CoA reductase inhibitors (statins):

- atorvastatin greater than 20 mg (see Allowed Medications, below)
- rosuvastatin greater than 10 mg (see Allowed Medications, below)
- fluvastatin, lovastatin, simvastatin (see Allowed Medications, below): The dose of fluvastatin, lovastatin, or simvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER. Statin-associated adverse events such as myopathy should be closely monitored.

The following medications/therapies may require dose adjustment or monitoring during the dosing period and for 14 days before and after the dosing period:

Co-administration with systemic tacrolimus increases the concentrations of tacrolimus. Therefore, frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration is recommended.

Other CYP3A4 substrates with narrow therapeutic ranges (e.g., alfentanil, astemizole, cisapride, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, terfenadine) are not prohibited, but their concentrations have the potential to be increased by approximately 30-40%. Therefore, subjects taking these medications should be monitored closely or dose adjusted appropriately.

In general, P-gp substrates with narrow therapeutic ranges (e.g., digoxin and colchicine) are not prohibited, but their levels have the potential to be increased. Therefore, subjects taking these medications should be monitored closely.

Investigational agents are not permitted.

Systemic corticosteroids (dose equivalent to ≥10 mg prednisone per day, except in the case of rapid steroid tapers<1 week in duration) are not permitted.

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

The following medications/therapies are allowed in this study:

Antihypertensives:

- Angiotension-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB): enalapril, captopril, lisinopril, ramipril, valsartan, losartan, telmisartan
- Beta blockers: atenolol, metoprolol, propranolol

Note: for other beta blockers, please consult with the Sponsor

- Calcium-channel blockers: verapamil, diltiazem, amlodipine

  Note: for other calcium-channel blockers, please consult with the Sponsor

- hydralazine, clonidine, minoxidil, isosorbide nitrates

Anemia: erythropoietin

Anticoagulants: warfarin, heparin, low molecular weight heparin, aspirin, fondaparinux, desirudin, acenocoumarol

Diuretics: HCTZ, furosemide, spironolactone, triamterene

Hypoglycemic agents: insulin, sitagliptin, glipizide, metformin

Contraceptives: oral contraceptive pills, progesterone injects, intrauterine devices

Antidepressants/anxiolytics: citalopram, paroxetine, duloxetine, escitalopram, fluoxetine, bupropion, trazodone, diazepam, clonazepam, temazepam, lorazepam

Acid reflux: H2 blockers, proton pump inhibitors, antacids

HMG-CoA reductase inhibitors (statins):

- pravastatin and pitavastatin: may be coadministered without dose adjustment
- rosuvastatin: the dose of rosuvastatin should not exceed a daily dose of 10 mg
- atorvastatin: the dose of atorvastatin should not exceed the daily dose of 20 mg
- fluvastatin, lovastatin, simvastatin: The dose of fluvastatin, lovastatin, or simvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.
- HIV/HBV medications: abacavir, dolutegravir, emtricitabine, entecavir, lamivudine, raltegravir, rilpivirine, tenofovir disoproxil fumarate

Immunosuppressants: prednisone, mycophenolate mofetil

Opiate substitution therapy: buprenorphine/naloxone, methadone

Antiarrhythmics: digoxin

Phosphate Binders

Note: For other medications not listed here, please consult with the Sponsor.

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

EBR/GZR can be taken with or without food.

Considerations for Study Visits

Procedure visits should be scheduled as close to the indicated study days and study weeks as possible. See the Trial Flow Chart (Section 6.0) for a complete listing of study procedures required at each visit.

Subjects should complete study therapy as defined by the length of the assigned treatment regimen. If dosing is missed or interrupted (see Section 5.2.2), the assigned study therapy regimens should still be completed.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5 – Trial Procedures.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

- The subject or legal representative (such as parent or legal representative) withdraws consent.
- Subject meets any HCV virologic failure criteria (see **Section 4.2.3.1.1.2**).
- Subject becomes pregnant during the trial.
- The investigator feels that it is in the best interest of the subject to discontinue.
- The subject's ALT or AST increases to >500 IU/L and is confirmed with repeat test within one week.
- The subject's ALT or AST increases to >3x the nadir value, is >3x ULN (confirmed with repeat test within one week), and there is a simultaneous increase in total bilirubin >2x ULN and/or INR is increased from the baseline value and is >1.5 (unless the subject is on anticoagulation).
- The subject's ALT or AST increases to >3x nadir, is >3x ULN (confirmed with repeat test within one week), and is temporally associated with signs or symptoms of liver inflammation that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to study therapy.

Clinical management of HIV-1 virologic failure will be handled by site investigators according to current HIV treatment guidelines and local standard of care. Subjects with HIV virologic failure may continue in the trial unless treatment with a prohibited concomitant medication (see Section 5.5) is required to construct a new HIV treatment regimen.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 - Trial Flow Chart and Section 7.1.5 – Trial Procedures for those procedures to be completed at each specified visit.

Subjects may be allowed to begin treatment again if deemed medically appropriate.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or legal representative (such as parent or legal representative) withdraws consent from the trial.
- The subject is lost to follow-up

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Treatment Arm	Screen	Treatment Period				Follow Up Period			Unscheduled Visits	
		Day	Week							
Arm 1: 8 weeks	SCR	1[1]	4	8	NA	FU4	FU12	FU24	HCV VFC Visit	Early DC Visit
Arm 2: 12 weeks	SCR	1[1]	4	8	12	FU4	FU12	FU24		
Visit Number	1	2	3	4	5	6	7	8	9	10
Visit Window	-45 d	NA	-7 to +7 d	-7 to +14 d	-7 to +14 d	-1 to +2 w	-2 to +2 w	-2 to +2 w	NA	NA
Administrative Procedures										
Informed consent	X									
Informed consent for FBR	X									
Inclusion/exclusion criteria	X	X								
Subject identification card	X									
Medical history	X									
Prior and concomitant medication review	X	X	X	X	X				X	X
Treatment randomization/allocation		X								
Review study medication diary		X	X	X	X					X
Clinical Procedures/Assessments										
PE	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]				X[2]
Height		X								
Weight	X	X								
Vital signs	X	X	X	X	X				X	X
Subject confirmation of birth control	X	X	X	X	X	X			X	X
Review AEs[3]	X	X	X	X	X	X	X	X	X	X

Treatment Arm	Screen	Treatment Period				Follow Up Period			Unscheduled Visits	
		Day	Week							
Arm 1: 8 weeks	SCR	1[1]	4	8	NA	FU4	FU12	FU24	HCV VFC Visit	Early DC Visit
Arm 2: 12 weeks	SCR	1[1]	4	8	12	FU4	FU12	FU24		
Visit Number	1	2	3	4	5	6	7	8	9	10
Visit Window	-45 d	NA	-7 to +7 d	-7 to +14 d	-7 to +14 d	-1 to +2 w	-2 to +2 w	-2 to +2 w	NA	NA
Laboratory Procedures/Assessments										
Coagulation	X	X	X	X	X	X	X	X	X	X
Chemistry & hematology	X	X	X	X	X	X	X	X	X	X
FSH[4]	X									
Urinalysis		X								
Urine pregnancy test[5] (female of childbearing potential only)	X	X	X	X	X	X[5]			X	X
HBV Evaluations[6]										
HBsAg	X	X	X	X	X	X	X	X		
Anti-HBc	X									
Anti-HBs	X									
HBV DNA	X	X	X	X	X	X	X	X		
HCV Evaluations										
HCV genotype determination	X									
Liver imaging	X[7]									
HCV RNA level[8]	X	X	X	X	X	X	X	X	X	X[9]
Plasma for HCV viral resistance and biomarkers[10]		X				X	X	X	X	X[9]
Blood for genetic analysis[11]		X								

Treatment Arm	Screen	Treatment Period				Follow Up Period			Unscheduled Visits	
		Day	Week							
Arm 1: 8 weeks	SCR	1[1]	4	8	NA	FU4	FU12	FU24	HCV VFC Visit	Early DC Visit
Arm 2: 12 weeks	SCR	1[1]	4	8	12	FU4	FU12	FU24		
Visit Number	1	2	3	4	5	6	7	8	9	10
Visit Window	-45 d	NA	-7 to +7 d	-7 to +14 d	-7 to +14 d	-1 to +2 w	-2 to +2 w	-2 to +2 w	NA	NA
HIV Evaluations										
HIV-1 serology	X									
HIV RNA and CD4+ T-Cell Counts (all subjects)[12]	X									
Drug Administration[13]										
EBR/GZR (open label)		X	X	X[14]	X[14]					

AE = adverse event; anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; DC = discontinuation; DNA = deoxyribonucleic acid; EBR = elbasvir; EOT = end of treatment; FBR = future biomedical research; FSH = follicle-stimulating hormone; FU = follow-up; GZR = grazoprevir; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IEC = independent ethics committee; IRB = institutional review committee; NA = not applicable; PE = physical examination; RNA = ribonucleic acid; SCR = screening; TW = treatment week; VFC = virologic failure confirmation

[1] Procedures on Day 1 should be performed prior to the first morning dose unless otherwise specified.

[2] A comprehensive PE will be performed at screening and baseline (Day 1). For all other visits, a focused PE will be conducted when clinically indicated.

[3] All AEs that occur after the consent form is signed but before randomization/allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of randomization/allocation through 14 days following discontinuation of study treatment, all AEs must be reported by the investigator. The reporting timeframe for AEs meeting any serious criteria is described in Section 7.2.3.1.

[4] For postmenopausal women only, defined as at least 12 months with no menses in women ≥ 45 years of age.

[5] Urine pregnancy test kits will be dispensed to female subjects of childbearing potential so that a pregnancy test can be performed 2 weeks after completing treatment. The test results must be provided to the investigator and/or site personnel at FU4. Subjects should be instructed to contact the investigator and/or site personnel immediately if the result of the self-pregnancy test is positive. A serum pregnancy test will be performed whenever a urine pregnancy test yields a positive result.

[6] HBsAg, anti-HBc, and anti-HBs will be assessed at screening in all subjects. For all anti-HBc positive subjects, HBV DNA will also be assessed at screening, and both HBV DNA and HBsAg will be monitored during the trial.

[7] For cirrhotic subjects only, imaging is required within 6 months of randomization to evaluate for hepatocellular carcinoma. If liver imaging within 6 months prior to Day 1 is not available, imaging is required during screening.

[8] Leftover main study plasma will be stored at the end of the study for future biomedical research if the subject consents to FBR.

[9] If a subject is a confirmed virologic failure during therapy (i.e., rebound, breakthrough), then the sample collection for HCV RNA and viral resistance/biomarker is not needed for the early discontinuation visit.

[10] Blood samples will be collected for HCV viral resistance testing at baseline, virologic failure confirmation visits, and all FU visits after virologic failure confirmation or after early study medication discontinuation if the subject has quantifiable HCV RNA. At the same time points, samples will be collected for proteomics, and metabolomics and other exploratory analysis. Leftover main study plasma will be stored at the end of the study for future biomedical research if the subject consents to future biomedical research.

[11] This sample will be drawn for *IL28B* genotyping and for planned analysis of the association between genetic variants in DNA and drug response. Data analysis will be limited to *IL28B* genotyping if the IRB/IEC does not approve of, or if there is a documented law or regulation prohibiting, the planned analysis of the association between DNA variations and drug response. Leftover extracted DNA will be stored for future biomedical research if the subject signs the optional FBR consent.

[12] Blood samples will be collected for HIV RNA and CD4+ T cell counts as part of the screening visit for all subjects; however, these samples will only be processed if the HIV-1 serology result is positive.

[13] Sites should dispense 3 open-label EBR/GZR blister cards at the Day 1 visit and 2 open-label EBR/GZR blister cards at each remaining dispensing visit. An unscheduled visit must occur to get additional drug if the subject will run out of study drug prior to the next scheduled visit. Subjects should complete study therapy for all study drug as defined by the length of the assigned treatment regimen. If dosing is missed or interrupted (see Section 5.2.2), the assigned study therapy regimen should still be completed.

[14] Subjects in Arm 1 (8-week treatment arm) will proceed to FU4 as TW8 is their EOT visit. Subjects in Arm 2 (12-week treatment arm) will proceed to FU4 as TW12 is their EOT visit.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC'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 willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria (see Section 5.1) will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

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

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

The investigator or qualified designee will discuss with the subject the necessity of not taking any concomitant medications or herbal preparations with known suspected hepatotoxic potential. All medications with known hepatotoxicity must be discontinued from 2 weeks prior to dosing through 2 weeks after dosing. If medications with potential hepatotoxicity cannot be discontinued in a subject, the principal investigator must discuss the inclusion of the subject with the Merck clinical director who must approve the use of the medication prior to inclusion of the subject in the trial.

7.1.1.6 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be either randomly allocated or assigned (in accordance with the trial design described in Section 2.1) and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

The investigator/study coordinator will give the subject a Study Medication Diary (SMD) to be completed during the study period. The investigation/study coordinator will be responsible for entering the subject's identification (treatment/randomization number), treatment period, and other pertinent subjection information before giving the SMD to the subject. The subject will be instructed to record dates/times and the number of tablets of study drug doses on the SMD for the entire time period. Only the subject should enter information on the SMD. The subject is to return the completed SMD at each scheduled visit. At visits when used/unused study drugs are returned, site personnel must verify the accuracy of the SMD by comparing entries with amounts of return study drugs. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the subject, and the explanation must be documented. Only the subject shall make any changes to the entries on the SMD. The subject will initial the SMD to confirm that the information accurate. The investigator/study coordinator will be responsible for transferring the appropriate information from the diary card onto the appropriate case report form (CRF).

Interruptions from the protocol specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication should be witnessed by the investigator and/or trial staff at the Day 1 visit.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

All physical examination must be performed by the principal investigator or sub-investigator (physician, physician assistant, or nurse practitioner).

A complete physical examination, performed at the Screening visit and on Day 1 includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic examinations should be performed when clinically indicated. For all other visits, a focused examination will be performed when clinically indicated. Any significant changes between the Screening visit and Day 1 should be noted in the Medical History electronic CRF (eCRF). Any significant changes after receiving study drug at Day 1 must be reported as AEs and entered on the AE eCRF. If a subject is discontinued for any reasons during the treatment period, every attempt should be made to perform a final physical examination.

7.1.2.2 Weight and Height Assessment

The subject's weight should be assessed as mentioned in the Trial Flow Chart (Section 6.0). Clinically significant changes from Day 1 should also be captured as AEs in the eCRF.

7.1.2.3 Vital Signs

Vital signs will include heart rate, blood pressure, and oral temperature. Subjects should be resting in a semi-recumbent or sitting position for at least 10 minutes prior to having vital sign measurements obtained.

NOTE: Oral temperatures should be taken, but if oral is not possible, a tympanic, rectal, or axillary temperature may be taken.

After the Screening visit, the site should indicate whether or not the result is clinically significant and if any subsequent changes constitute an AE.

7.1.2.4 Birth Control Confirmation

Extreme care must be taken to avoid pregnancy in female subjects of childbearing potential.

Confirmation must be obtained by site personnel that subjects are using acceptable methods of contraception (see Subject Inclusion Criteria, Section 5.1.2). This assessment must be documented in the subject's study chart at each specified visit.

7.1.2.5 Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 13. The investigator's assessment of causality is required for each adverse event. Refer to Table 13 for instructions in evaluating adverse events.

7.1.2.6 Noninvasive Methods of Cirrhosis Evaluation

FibroScan®: This method for assessing liver cirrhosis has gained increasing acceptance. In the US, this methodology is FDA approved and in other countries it is often the preferred method of assessment. FibroScan® results are influenced by a number of confounders including ALT, ascites, and underlying disease. Hepatitis C is one of the best studied and is the disease state with the most reproducible/reliable results. FibroScan® has been evaluated in many liver diseases for the staging of liver fibrosis, and has been demonstrated to be very effective for differentiating cirrhosis (F4) from no cirrhosis (< F4), but it is less capable of differentiating gradations of fibrosis. In a large study by Castera, et al [30], a population of patients with chronic hepatitis C, a cutoff of 12.5 kPa was selected for cirrhotics. At this cutoff, the sensitivity and specificity of the test for cirrhosis were 87% and 91%, respectively and the negative predictive value was 95%. Since this analysis was assessed specifically in patients with chronic hepatitis C, the cutoff value > 12.5 kPa used by Castera was selected to include cirrhotics in the current study.

FibroTest® + APRI: Various methodologies have been developed in order to improve the sensitivity and specificity of blood tests used to diagnose cirrhosis in patients with chronic hepatitis C infections. One such algorithm, the Sequential Algorithm for Fibrosis Evaluation (SAFE), which uses a combination of FibroTest® and the aspartate aminotransferase-to-platelet ratio index (APRI) is very accurate for diagnosing cirrhosis [31]. For cirrhosis, the SAFE for F4 algorithm provides a diagnostic accuracy of 89.5% with a negative predictive value of 94.6%. Using this algorithm, it is estimated that only 6.2% of the patients would need a liver biopsy to confirm the diagnosis of cirrhosis. The cutoff values for excluding cirrhotics using the 2 tests, without the use of liver biopsy, are ≤1 and ≤0.48 for FibroTest® and APRI when the SAFE for F4 is used. This study uses this method with one variation and that is the more stringent requirement that both the APRI and FibroTest® need to be consistent with no cirrhosis (i.e., APRI is ≤1 AND FibroTest® ≤0.48). Accordingly, the Sponsor is confident these cutoff values that will differentiate cirrhotic from non-cirrhotic patients with reasonable accuracy in this study.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided as follows. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject, can be found in Section 12.5.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 12.

All screening laboratory results must be reviewed and approved before a subject can be assigned or randomly assigned to study medication. Sample collection, storage and shipment instructions will be provided in the operations/laboratory manual.

Table 12 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Bilirubin	
Hemoglobin	ALP	Blood	HCV genotype
Platelet count	ALT	Glucose	FSH
WBC count (total and differential)	AST	Ketones	Prothrombin time (PT)
Erythrocytes (RBC count)	Creatinine	Leukocyte esterase	INR
	Creatine kinase	Nitrite	Choriogonadotropin beta (urine pregnancy test kits to sites)
	GGT	pH	Serum human chorionic gonadotropin (reflex when urine pregnancy test is "positive")
	Glucose (serum glucose)	Protein	Plasma HCV RNA
	Amylase	Specific gravity	FibroSure® (FibroTest®) as requested by site for entry criteria [may be performed locally])
	Lipase	WBC	APRI calculation (screening only)
	Potassium	Bacteria	HIV-1 and HIV-2 serology (screening only)
	Sodium		CD4 T-cell count (HIV positive subjects)
	Total bilirubin	Squamous epithelial cells	HIV RNA viral load (HIV positive subjects)
	Direct bilirubin	RBC	HBsAg (at screening in all subjects, then at certain subsequent visits for subjects who are anti-HBc positive)
	Indirect bilirubin		Anti-HBc (screening only)
	Total protein		Anti-HBs (screening only)
	BUN		HBV DNA (for subjects who are anti-HBc positive, at screening and at certain subsequent visits)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; Anti-HBc = hepatitis B core antibody; Anti-HBs = hepatitis B surface antibody; APRI = AST-to-platelet ratio index; AST = aspartate aminotransferase; BUN = blood, urea, nitrogen; FSH = follicle-stimulating hormone; GGT = gamma-glutamyltransferase; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = International Normalized Ratio; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cell.

7.1.3.2 HCV Evaluation

The following specimens are to be obtained for HCV evaluation as part of efficacy/pharmacogenetic measurements:

- Samples for HCV genotype evaluation must be obtained for inclusion in the study. All baseline samples will be genotyped using the FDA-approved Abbot HCV Real Time Genotype II assay that detects HCV genotypes 1a, 1b, 2, 3, 4, 5, and 6 through the use of genotype-specific fluorescent-labeled oligonucleotide probes in a real-time PT-PCR assay. The RT-PCR reaction uses 3 sets of HCV-specific amplification primers targeting the 5'UTR (for all genotypes) and NS5B regions from GT1a and 1b. The assay has accuracy of > 96% for GT1, 1a, 1b, 2, 3, and 5; 89% for GT5, and 83% for GT6; with 100% specificity in HCV serologically negative plasma samples.
- Blood must be drawn from each subject to assess HCV RNA plasma levels at various time points as shown in the Trial Flow Chart (Section 6.0). HCV RNA in plasma will be measured using a COBAS™ AmpliPrep/COBAS™ Taqman HCV Test, version 2.0® assay with a lower limit of quantification (LLOQ) of 15 IU/mL. Leftover plasma may be used for viral resistance testing if needed. Also, leftover plasma may be used for FBR only if the subject signed for FBR consent.
- Blood must be drawn from each subject to assess viral resistance mutation and processed as instructed by the central laboratory manual. Leftover plasma may be used for FBR only if the subject signed for FBR consent.
- Protein and metabolites may be measured from blood samples to compare biomarkers measured prior to treatment, to biomarkers measured at several time points during treatment that correlate with subject response to treatment (e.g., sustained viral response).
- Samples collected for genetic analysis are obtained at Day 1. Any leftover deoxyribonucleic acid (DNA) may be used for FBR only if the subject sign for FBR consent.

NOTE: Samples may also be used for future assay development and validation if the subject signed for FBR consent.

7.1.3.3 HIV Evaluation

The following specimens are to be obtained for HIV evaluation:

- Blood must be drawn from each subject to assess HIV RNA plasma levels at screening as shown in the Trial Flow Chart (Section 6.0). HIV RNA in plasma will be measured using a COBAS™ AmpliPrep/COBAS™ TaqMan HIV-1 Test, version 2.0® assay with a LLOQ of 20 IU/mL.
- Blood must be drawn from each subject to assess immunologic status. CD4+ T-cell counts will be obtained at screening as shown in the Trial Flow Chart (Section 6.0).

The following nomenclature will be used when describing HIV RNA levels:

- HIV-1 RNA < LLOQ, Target Not Detected
- HIV-1 RNA < LLOQ, Target Detected
- HIV-1 RNA IU/mL

7.1.3.4 HBV Evaluation

- Blood must be drawn from each subject to assess HBsAg, anti-HBc, and anti-HBs at screening.
- For subjects who are anti-HBc positive, HBV DNA will be assessed at screening, and both HBV DNA and HBsAg will be monitored during the trial. The results of these assessments will be used to determine HBV reactivation, which will be reported as an Event of Clinical Interest as specified in Section 7.2.3.2.
- Subjects who develop HBV reactivation will be managed by site investigators according to current treatment guidelines and/or local standard of care.
- Subjects who develop HBV reactivation may continue in the trial at the discretion of the site investigators

7.1.3.5 Planned Genetic Analysis Sample Collection

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

7.1.3.6 Future Biomedical Research Sample Collection

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

Leftover DNA for future research; leftover plasma from HCV RNA for future research; and leftover plasma from viral resistance and biomarkers for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), 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 trial data and results. No new analyses would be generated after the request is received.

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Equipment

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

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Up to 45 days prior to randomization/treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Verification should be obtained to confirm the subject's cirrhosis status and the subject's fibrosis score must be captured to support secondary data analysis.

Documentation of prior IFN +/- RBV +/- SOF treatment history must include clinic notes or referral letter documenting regimen administered, approximate dates of treatment, approximate date of virologic failure, and a history of laboratory confirmed prior virologic

failure or documented intolerance to allow for one of the following categorizations (if the subject was treated with a PR regimen more than once, the categorization must be based on the most recent round of treatment)**:**

1. HCV Treatment-Naïve: defined as no prior exposure to any interferon, ribavirin, or other approved or experimental HCV-specific direct-acting antiviral agent.
2. HCV Treatment-experienced: defined as any prior treatment with an IFN regimen (IFN or peg-IFN +/- RBV) or sofosbuvir (SOF) + RBV or SOF + peg-IFN + RBV that did not result in a sustained virologic response (SVR)

   All TE patients will be classified into one of the following categories:

   I. Prior On-Treatment Failures (may be one or more of the following):

      i. Non-Responder: Subject has HCV RNA detected at end of prior treatment without HCV RNA <LLOQ on treatment.

      ii. Null Responder: <2 log10 IU/mL reduction in HCV RNA after at least 12 weeks of a IFN regimen OR <1 log10 IU/mL reduction in HCV RNA after 4 weeks and discontinued therapy prior to treatment-week 12.

      iii. Breakthrough: Subject has a confirmed HCV RNA ≥LLOQ [TD(q)] while on prior treatment after being <LLOQ previously.

      iv. Partial Responder: ≥2 log10 IU/mL reduction in HCV RNA after at least 12 weeks of treatment, but not achieving HCV RNA target not detected at end-of-treatment, with prior regimen.

   II. Relapser: HCV RNA target not detected at end-of-treatment after prior regimen, but HCV RNA quantifiable (≥ LLOQ) during follow-up.

   III. Intolerant to Prior Regimen: ≥ 4 weeks of prior regimen and no more than 80% of treatment duration:

      1. ≤ 20 weeks for a 24 week treatment regimen
      2. ≤ 40 weeks for a 48 week treatment duration

   IV. Otherwise not Classified/Unknown response to Prior Regimen: Subject received at least one dose of prior regimen and stopped for any other reason not listed above

The investigator will discuss with each potential subject the nature of the study, its requirements, and its restrictions. Screening procedures may be repeated after consultation with the Sponsor.

Subjects will be instructed that they are required to use an acceptable method of birth control (see Subject Inclusion Criteria Section 5.1.2) from at least 2 weeks prior to Day 1, throughout treatment, and 14 days after the last dose of study medication, or longer if dictated by local regulations, for women and men, respectively.

Subjects will be instructed about the restrictions for concomitant medications, as noted in Section 5.5.

All screening procedures listed for Visit 1 in the Trial Flow Chart must be completed and subject eligibility confirmed by the investigator prior to the subject's randomization/allocation and drug administration.

All subjects will be given a Subject Identification Card (Section 7.1.1.3), at the time of screening, identifying them as participants in a research study. The Subject Identification Card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

7.1.5.2 Rescreening

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

- HCV GT determination
- Hepatitis B virus screening
- HIV-1 serology
- Liver biopsy/FibroScan®/ FibroSure® (FibroTest®)
- Liver imaging

If any of the laboratory exclusion criteria are met, the site may have the abnormal value retested one time, except as prohibited in exclusion criterion 13.

7.1.5.3 Treatment Period

Day 1 procedures listed on the Trial Flow Chart should be performed prior to dosing unless specified otherwise. For female subjects, a urine pregnancy test will be performed at the site prior to study drug initiation. If the urine pregnancy test result is negative, the subject will be eligible for randomization/allocation and the remainder of the pretreatment (Day 1) testing/procedures will be performed. If the urine pregnancy test result is positive, a serum pregnancy test will be performed. If the result of the serum pregnancy test is positive, the subject must not be randomized/allocated to study medication.

Blood and urine will be collected for assay of safety evaluations, plasma HCV RNA, plasma HIV RNA. These samples will be sent to the appropriate central laboratory following the procedure(s) set forth in the manual(s).

Additional samples will be collected for genetic evaluation of host parameters related to the response of HCV subjects to EBR/GZR (as appropriate) therapy.

Subjects should complete study therapy for all study drugs as defined by the length of the assigned treatment regimen. If dosing is missed or interrupted (see Section 5.2.2), the assigned study therapy regimen should still be completed.

7.1.5.4 Drug Administration

Following completion of the Day 1 procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the IVRS for assignment of the drug regimen to be administered and duration of treatment. Sites should not call IVRS for drug administration until the subject has met all criteria for the study and are ready to receive the first dose of study medication on Day 1.

The first dose of prescribed study medications should be administered at the Day 1 visit.

Subjects who discontinue therapy in the trial prior to the last scheduled treatment visit should have an Early Discontinuation visit and then continue into follow-up visits.

At a minimum, collect the following information when a subject discontinues:

- The reason the subject discontinued
- The date of the last dose of study medications from the trial
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate
- (Serious) Adverse events

Final Assessments:

- Every effort should be made to ensure that all procedures and evaluations scheduled for the Early Discontinuation Visit are performed.
- Retrieve all study medications from the subject.

7.1.5.5 Follow-Up Visits

At the completion of study therapy subjects will return to the study site for follow-up visits at 4, 12, and 24 weeks after the last dose of study drug.

Subjects who discontinue because they have met criteria for virologic failure (Section 4.2.3.1.1.2) while on study therapy should complete an Early Discontinuation Visit as outlined in the Trial Flow Chart (Section 6.0), and return to the study site for follow-up visits at 4, 12, and 24 weeks following confirmation of virologic failure. Subjects who meet the virologic failure criterion for relapse (HCV RNA ≥ LLOQ following the end of all study therapy, after becoming undetectable [TND] at the end of treatment) will return to the study site for the remainder of their follow-up visits (e.g., 4, 12, and 24 weeks) as outlined in the Trial Flow Chart (Section 6.0).

Subjects who discontinue for reasons other than virologic failure should complete an Early Discontinuation Visit as outlined in the Trial Flow Chart and return to the study site for follow-up visits at 4, 12, and 24 weeks following the discontinuation of treatment.

7.1.5.6 Evaluation of Laboratory Safety Signals

Laboratory safety measurements will be evaluated throughout the study to assess potential liver safety signals as outlined in the Trial Flow Chart (Section 6.0).

If a subject has one or more of the laboratory ECI criteria (see Section 7.2.3.2) at the last dosing visit, then the subject should return to the site weekly for additional monitoring until the values normalize.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. 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.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

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

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 13 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's 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 the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. first instance of ALT or AST >500 IU/L from the initiation of study therapy through 14 days following treatment.*
3. first instance of ALT or AST >3X nadir AND >3X ULN from the initiation of study therapy through 14 days following treatment. *

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

4. HBV reactivation defined as either:
   a. sero-reversion from HBsAg negative to HBsAg positive, OR
   b. detectable HBV DNA in subjects who were previously undetectable or ≥1 log increase in HBV DNA from baseline.

   Note: As detailed in Section 7.1.3.4, subjects who develop HBV reactivation will be managed by site investigators according to current treatment guidelines and/or local standard of care. Subjects who develop HBV reactivation may continue in the trial at the discretion of the site investigators.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 13. The investigator's assessment of causality is required for each adverse event. Refer to Table 13 for instructions in evaluating adverse events.

Table 13 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and 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 event when, based upon appropriate medical judgment, the event may jeopardize the subject 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 event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is provided in 8.2-8.12.

Study Design Overview	A Multi-Site, Open-Label, Partially-Randomized Trial of the Efficacy and Safety of Fixed Dose Elbasvir/Grazoprevir (EBR/GZR) Based Regimens in French Subjects with Chronic Hepatitis C Virus (HCV) Genotype 4 Infection
Treatment Assignment	This study will enroll approximately 120 genotype 4 (GT4) HCV subjects with or without advanced fibrosis. There are 2 treatment arms in this study. Approximately 75 (minimum of 60) TN subjects with stage 0-2 fibrosis will be randomized using a 2:1 ratio to receive either 8 weeks of EBR/GZR (Arm 1) or 12 weeks of EBR/GZR (Arm 2). TN subjects with stage 3-4 fibrosis and TE subjects with stage 0-4 fibrosis will be assigned to Arm 2 to receive 12 weeks of EBR/GZR. The target enrollment in each group is: Study Arm 1: 8-week regimen of EBR/GZR TN subjects with fibrosis stage F0-F2 n=50 (min 40) Study Arm 2: 12-week regimen of EBR/GZR TN subjects with fibrosis stage F0-F2 n=25 (min 20) TN subjects with fibrosis stage F3-F4 n=25 (min 15) TE subjects with fibrosis stage F0-F4 n=20 (min 15)
Analysis Populations	Efficacy: The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all subjects who were assigned to a treatment arm and received at least one dose of study treatment. A supportive analysis using the modified Full Analysis Set (mFAS) population will be performed for the primary efficacy and secondary endpoints. The mFAS population is a subset of the FAS, with subjects excluded for study discontinuation (lost to follow-up) with reasons unrelated to the treatment regimen. Safety: The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least one dose of study treatment, classified according to the study treatment duration they actually received.

Primary Endpoint(s)	Proportion of subjects achieving SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy).
Key Secondary Endpoints	Proportion of subjects achieving SVR_{24} (Sustained Virologic Response 24 weeks after the end of all study therapy).
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	A 2-sided 95% confidence interval (CI) based on Clopper-Pearson method will be constructed for the proportion of subjects achieving arm-specific SVR_{12} and SVR_{24}, and for treatment naïve F0-F2 subjects achieving arm-specific SVR_{12}. There will be no efficacy hypothesis testing conducted in this estimation study.
Statistical Methods for Key Safety Analyses	The proportion of subjects who experienced adverse events of elevated laboratory values that are reported as ECIs during the study therapy period will be estimated along with the corresponding 95% confidence intervals based on Clopper-Pearson method. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized.
Interim Analyses	No interim analyses are planned for this study.
Multiplicity	There will be no multiplicity adjustments in the final analysis of this estimation study.
Sample Size and Power	Approximately 120 subjects will be enrolled with approximately 50 in Arm 1 (8 week treatment) and 70 in Arm 2 (12 week treatment). The 95% CI and half-width of the 95% CI for SVR_{12}, under various scenarios, is presented in Table 17. For example, when the sample size is 25, if the SVR_{12} rate is 92.0% (23 successes out of 25), the exact 95% CI is (74.0%, 99.0%). When the sample size is 50, if the SVR_{12} rate is 90.0% (45 successes out of 50), the exact 95% CI is (78.2%, 96.7%). When the sample size is 70, if the SVR_{12} rate is 90.0% (63 successes out of 70), the exact 95% CI is (80.5%, 95.9%).

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics of the Sponsor. Certain specific analyses such as resistance will be the responsibility of the appropriate department of the Sponsor.

This study will be conducted as a partially randomized and open-label study; therefore, the subjects, the study site personnel, and the Sponsor will be aware of subject treatment assignments after each subject is enrolled.

Throughout the course of this partially randomized and open-label study, efficacy and safety analyses may be performed by the Clinical Biostatistics department of the Sponsor to monitor trends and facilitate programmatic decisions.

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. There will be no efficacy hypothesis testing conducted in this estimation study.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed as follows.

8.4.1 Efficacy/Pharmacokinetics Endpoints

8.4.1.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.2.3.1.

The primary efficacy endpoint is the proportion of subjects achieving SVR_{12} (sustained virologic response 12 weeks after the end of all study therapy), defined as HCV RNA <LLOQ (either TD[u] or TND).

The secondary efficacy endpoints are:

- The proportion of subjects achieving SVR_{12}, defined as HCV RNA < LLOQ (either TD[u] or TND) in the treatment-naïve F0-F2 subjects.
- The proportion of subjects achieving SVR_{24} (sustained virologic response 24 weeks after the end of all study therapy), defined as HCV RNA < LLOQ (either TD[u] or TND).
- The viral resistance-associated variants (RAVs) resistant to EBR or GZR, including the association of baseline RAVs with treatment outcomes (SVR_{12} and SVR_{24}) and the emergence of RAVs in subjects who fail to achieve SVR.

8.4.1.2 Exploratory Endpoints

The exploratory efficacy endpoints are:

- To explore the relationship between *IL28B* genetic variation and:
  - SVR_{12}
  - SVR_{24}
- The relationship between genetic variation and the clinical response to the treatments administered.
- The proportion of anti-HBc positive subjects at screening who develop HBV reactivation (see Section 7.2.3.2).

8.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.3.2 and events of clinical interest (ECIs) are defined in Section 7.2.3.2. The proportion of subjects who experience AEs of elevated laboratory values that are reported as ECIs described in Section 7.2.3.2 during the study therapy period will be estimated.

The following events will also be investigated: the proportion of subjects with adverse events of the following types at any time during the study therapy period: (1) at least one adverse event; (2) a drug-related adverse event; (3) a serious adverse event; (4) a serious and drug-related adverse event and (5) an adverse event leading to discontinuation.

Other safety parameters include vital signs, physical examinations, and standard laboratory safety tests at time points specified in the Trial Flow Chart (Section 6.0).

Drug related serious adverse events will continue to be collected throughout the study.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Population

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all subjects who were assigned to a treatment arm and received at least one dose of study treatment.

A supportive analysis using the modified Full Analysis Set (mFAS) population will be performed for the primary (SVR_{12}) and key secondary efficacy endpoint (SVR_{24}). The mFAS population is a subset of the FAS, with subjects excluded for study discontinuation (lost to follow-up) with reasons unrelated to the treatment regimen. Examples of reasons for the exclusion of a subject include: failure to receive at least one dose of study treatment; loss to follow-up; missing data due to death with reasons unrelated to the study drug; discontinuation due to non-drug related AEs; informed consent and withdrawal.

Resistance Analysis (RA) Population will be used for resistance-associated variants (RAVs) analysis. The RA population is a subset of FAS, who either achieved SVR_{12} or met criteria for virologic failure (see Section 4). The RA does not include any subject who discontinued the study for reasons other than virologic failure. Baseline RAV analyses will be conducted in subjects for whom baseline sequencing data was available. Post-baseline RAV analyses will be limited to subjects who had both baseline and post-failure sequence data.

Details on the approach to handling missing data are provided in Section 8.6.1.

8.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least one dose of study treatment. Subjects will be included in the treatment arm corresponding to the study treatment durations they actually received for the analysis of safety data using the ASaT population. The subjects who receive 9 weeks of treatment or less will be summarized in Arm 1 and subjects who receive longer than 9 weeks of treatment will be summarized in Arm 2 for the purposes of safety. Subjects who withdraw study drug early during the treatment period will be included in the treatment arm based on the study treatment duration they actually received.

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

Details on the approach to handling missing data for safety analyses are provided in Section 8.6.2 Statistical Methods for Safety Analyses.

8.6 Statistical Methods

The approach to handling missing data for efficacy analyses is described in Section 8.6.1. A summary of the analysis strategy for efficacy variables is shown in Table 14. Nominal p-values may be computed for some efficacy analyses as a measure of strength of the association but no tests of hypotheses are planned in this estimation study. The analysis strategy for safety is described in Section 8.6.2.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

Missing Values

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

The HCV RNA outcome is categorized as TND (Target not detected), TD(u) (Target detected but unquantifiable), and TD(q) (Target detected, quantifiable). There are 3 types of missing data handled by different approaches.

Type 1 is intermittent missing:

- Intermittent missing: If a missing data point is immediately preceded and followed by non-missing HCV RNA outcomes, the missing value would be imputed to the worst outcome of the two. For example, if a missing data point is preceded by TD(q) and followed by TD(u) or TND, then the missing value would be imputed as TD(q); if a missing data point is preceded by TD(u) and followed by TND, then the missing value would be imputed as TD(u); when a missing value is flanked by 2 TNDs, then the missing value would be imputed as TND.

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

- Type 2 – Non-intermittent missing related to the study drug: For missing values due to premature study discontinuations due to treatment related reasons either for safety or efficacy, the missing values will be considered as treatment failures.
- Type 3 – Non-intermittent missing unrelated to the study drug: For missing data due to premature study discontinuations with reasons unrelated to treatment such as loss to follow-up, protocol violation, withdrawal of consent, administrative reasons, etc., the missingness mechanism is unlikely to be related to subjects' response to the HCV treatment, and therefore the missing at random (MAR) assumption is reasonable. The approaches to address this type of missing data depend on the analytical strategy, and these are described as follows.

The following 2 approaches will be used to handle non-intermittent missing data (Type 2 and 3) due to premature discontinuations, depending on the analytical strategy, as described in the following section and Table 14 Analysis Strategy for Efficacy Variables.

- Treatment-Related Discontinuation = Failure (TRD=F) approach: The treatment related type 2 missing will be considered as failure; whereas the subjects who have the type 3 missing value and do not have virologic failure during the observed study period will be excluded from the analysis for the time points following their study withdrawal. Note that subjects with documented virologic failure during the treatment or follow-up period, even if they withdrew prematurely due to reasons not related to study drug, are classified as failures.
- Missing=Failure (M=F) approach: Any non-intermittent missing (i.e., type 2 and 3 missing) will be imputed as failure, regardless of the reason for study discontinuation.

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

Proportion of Subjects With Virologic Responses

For the primary efficacy analysis based on the FAS population to estimate the proportions of subjects achieving SVR_{12}, 95% confidence intervals for these rates will be calculated using the Clopper-Pearson method [32] within treatment arms with no stratification. The missing data approach of M=F described above will be utilized for the primary analysis. The same method will be used to analyze all binary endpoints based on the FAS population.

The SVR_{12} rates and confidence intervals for the randomized treatment-naïve F0-F2 subjects who received either 8 weeks of treatment or 12 weeks of treatment will be interpreted in the context of the historical clinical experience with EBR/GZR.

Sensitivity analyses will be performed for the primary endpoint and key secondary endpoint using the mFAS population with the TRD=F missing data approach. Under the assumption of missing completely at random (MCAR), the mFAS population excludes subjects who did not experience virologic failure, but prematurely withdraw from study due to reasons not related to the study drug (i.e., the subjects with the type 3 missing value). Note that subjects with documented virologic failure during the treatment or follow-up period, even if they withdrew prematurely due to reasons not related to study drug, are included in the mFAS population and classified as failures.

Table 14 summarizes the key efficacy analyses and Table 15 includes additional information on criteria to assess the primary endpoint (SVR_{12}) and key secondary endpoint (SVR_{24}).

Table 14 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Proportion of subjects achieving SVR_{12} in each treatment arm	P	95% CI (Clopper-Pearson)	FAS	M=F
Proportion of subjects achieving SVR_{12} in each treatment arm	S	95% CI (Clopper-Pearson)	mFAS	TRD=F
Secondary				
Proportion of subjects achieving SVR_{24} in each treatment arm	P	95% CI (Clopper-Pearson)	FAS	M=F
Proportion of subjects achieving SVR_{24} in each treatment arm	S	95% CI (Clopper-Pearson)	mFAS	TRD=F
CI = confidence interval; M=F = Missing=Failure; P = Primary approach; S = Secondary approach; TRD=F = Treatment-Related Discontinuation=Failure.				

Table 15 Analysis Populations, Criteria for Response, Non-Response, and Exclusion from Analysis Population

Analysis Population	Criteria for Response	Criteria for Non-Response	Criteria for Exclusion From Analysis Population
FAS	HCV RNA < LLOQ	HCV RNA ≥LLOQ	Subject did not receive at least one dose of study medication
mFAS	HCV RNA < LLOQ for baseline infection[†]	HCV RNA ≥LLOQ for baseline infection	Subject discontinued from the study for non-treatment related reasons. Examples include: Loss to follow-up; d/c due non-drug related AEs; informed consent withdrawal.
FAS = full analysis set; HCV = hepatitis C virus; LLOQ = lower limit of quantification; mFAS = modified full analysis set; RNA = ribonucleic acid. [†] This includes the case where HCV RNA ≥ LLOQ but is demonstrated to be due to reinfection (after clearance of baseline infection)			

Subject Virologic Failure: Non-response, Rebound, Virologic Breakthrough and Relapse

Summary statistics will be provided to describe the rates of occurrence of subject non-response, rebound, virologic breakthrough, and relapse. Definitions for subject virologic non-response, rebound, breakthrough, and relapse are in Section 4.2.3.1.1.2.

8.6.2 Statistical Methods for Safety Analyses

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

The proportion of subjects with adverse experiences of elevated laboratory values that are reported as ECIs described in Section 7.2.3.2 during the study therapy period are prespecified as events of clinical interest and will be provided.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized in the same manner (Table 16). Laboratory parameters will be summarized by pre-defined limits of change, laboratory grade shift summaries, and for selected laboratory parameters, change from baseline summaries.

In this estimation study, rates of events of clinical interest (as defined in Section 7.2.3.2) as well as broad categories of adverse events will be reported along with 95% confidence intervals for safety monitoring. Rates will also be shown for all specific AEs reported and pre-determined limits of change in laboratory results.

Missing safety parameter values will be handled using the Data-As-Observed (DAO) approach, that is, any missing value will be excluded from the analysis. For lab shift summaries, change from baseline summaries and certain pre-defined limits of change summaries require a baseline value. If a baseline value is missing, the latest pre-treatment value will be used instead. If no pre-treatment result is available, that subject will not be included in the summary. The safety summarization of results will be presented by treatment arm (Arm 1 and Arm 2) unless otherwise specified.

Table 16 Analysis Strategy for Safety Parameters

Safety Endpoint[†]	95% CI[‡]	Descriptive Statistics
AEs of elevated laboratory values that are reported as ECIs	X	X
Any AE	X	X
Any SAE	X	X
Any drug-related AE	X	X
Any serious and drug-related AE	X	X
Discontinuation due to AE	X	X
Specific AEs, SOCs, or PDLCs		X
Change from baseline results (laboratory results, vital signs)		X

AE = adverse event; CI = confidence interval; ECI = clinical event of interest; PDLC = pre-defined limit of change; SOC = system organ class; X = results will be provided.
[†] Adverse experience references refer to both clinical and laboratory AEs.
[‡] 95% CIs are provided for selected endpoints in this estimation study for safety monitoring.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, enrolled, the primary reasons for screen failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, and genotype subtype), primary and secondary diagnoses, and prior and concomitant therapies will be summarized using descriptive statistics for continuous or categorical variables, as appropriate. Summary statistics for the baseline efficacy measure (HCV RNA) will also be provided.

Viral Resistance Measurements

Viral resistance testing will focus on the entire NS3/4A and NS5A regions for all subjects and for those who meet the subject virologic failure criteria (see Section 4.2.3.1.1.2).

8.7 Interim Analysis

No interim analyses are planned for this study.

8.8 Multiplicity

There will be no multiplicity adjustments in the analyses of this study.

8.9 Sample Size and Power Calculation

An initial description of sample size is provided in Section 4.2.1.6.

The expected sample size for each treatment arm in this study (N=50, and 70) was selected based on the knowledge of the epidemiology of HCV infection in France. This is an exploratory study and the samples sizes are reflective of the number of patients that are likely to be enrolled in each treatment arm and are not driven by statistical consideration.

8.9.1 Sample Size and Power for Efficacy Analysis

This is an estimation study; no statistical testing will be performed for the efficacy endpoints. In this study, approximately 120 subjects will be enrolled with expected 50 subjects (minimum of 40) in Arm 1, and 70 in Arm 2.

Because of the differing subject populations and treatment regimens being administered in each study arm, differing response rates may be expected in each group. Table 17 shows 2-sided 95% CIs for SVR_{12} under varying assumptions of the number of observed successes for the FAS population corresponding to the different expected response rates for a group. Confidence intervals are based on the expected sample size. If the actual sample size is smaller, the CI for a given observed rate will be wider. Note that the intervals are not symmetric around the point estimate. The width of the 95% CIs are also provided to give an estimate of the precision of each estimated SVR_{12} rate.

Table 17 Two-Sided 95% Confidence Intervals for SVR12

N	Expected Response Rate	Observed Number of Subjects Achieving SVR_{12} (%)	95% CI†	Width of 95% CI (percentage points)
25	88%	22 (88.0%)	(68.8, 97.5)	28.7
	92%	23 (92.0%)	(74.0, 99.0)	25.0
	96%	24 (96.0%)	(79.6, 99.9)	20.3
50	90%	45 (90.0%)	(78.2, 96.7)	18.5
	92%	46 (92.0%)	(80.8, 97.8)	17.0
	94%	47 (94.0%)	(83.5, 98.7)	15.2
	96%	48 (96.0%)	(86.3, 99.5)	13.2
	98%	49 (98.0%)	(89.4, 99.9)	10.5
70	90%	63 (90.0%)	(80.5, 95.9)	15.4
	92%	65 (92.9%)	(84.1, 97.6)	13.5
	95%	67 (95.7%)	(88.0, 99.1)	11.1
	97%	68 (97.1%)	(90.1, 99.7)	9.6
	98%	69 (98.6%)	(92.3, 100.0)	7.7

†Confidence intervals are based on the expected sample size. If the actual sample size is smaller, the CI for a given observed rate will be wider.

8.9.2 Sample Size and Power for Safety Analysis

The primary safety objective of this study will be assessed by a review of the accumulated safety data. Certain safety endpoints of special interest have been identified in Section 8.4.2.

The estimate of the upper bound of the 95% confidence interval for the underlying percentage of subjects with a specific adverse event given various hypothetical observed number of subjects with that specific adverse event within any of the treatment groups is provided in Table 18. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [32].

Table 18 Estimate of Incidence of a Specific Adverse Event and 95% Upper Confidence Bound Based on a Hypothetical Number of Subjects with that Specific Adverse Event

n	Hypothetical Number of Subjects with Adverse Event	Observed Estimate of Incidence Rate	95% Upper Confidence Bound†‡
50	0	0.0%	7.1%
	1	2.0%	10.6%
	2	4.0%	13.7%
	3	6.0%	16.5%
	4	8.0%	19.2%
	5	10.0%	21.8%
	6	12.0%	24.3%
70	0	0.00%	5.1%
	1	1.43%	7.7%
	2	2.86%	9.9%
	3	4.29%	12.0%
	4	5.71%	14.0%
	5	7.14%	15.9%
	6	8.57%	17.7%
	7	10.00%	19.5%

† Based on the Clopper-Pearson method
‡ The 95% upper confidence bounds are based on the expected sample size. If the actual sample size is smaller, the upper bound for a given observed rate will be larger.

8.10 Subgroup Analyses and Effect of Baseline Factors

To assess the consistency of the response across various subgroups, the SVR_{12} rate with 95% CIs will be estimated within each category of the following classification variables listed below. The subgroups will be presented within each treatment arm (Arm 1 and Arm 2).

- Race (White, Black, Asian, Other)
- Sex (Female, Male)
- Age (≥ 65 years, < 65 years)
- *IL28B* genotype (CC vs. non-CC)
- HCV RNA at baseline:
  - ≤800,000 IU/mL versus >800,000 IU/mL
  - ≤2 million IU/mL versus >2 million IU/mL
  - ≤10 million IU/mL versus >10 million IU/mL
- Presence or absence of baseline NS3 and NS5A or both RAVs to any of the class of drugs used
- Cirrhosis status (Non-cirrhotic [fibrosis stage F0-F3] versus cirrhotic [F4])
- Fibrosis stage (F0-F2 vs F3-F4) by prior treatment history (TN or TE)

- Prior treatment history (see Section 7.1.5 for definitions):
  - treatment-naïve (TN) versus treatment-experienced (TE)
  - Among treatment-experienced (TE):
    - Relapse versus non-relapse
- Genotype 4 subgroup (4a, 4d, Other)

In addition, for the randomized subjects, SVR_{12} rates by HCV RNA at baseline (≤800,000 IU/mL versus >800,000 IU/mL) will be presented by treatment arm. Additional subgroup analysis summaries for the randomized subjects with regard to other factors may be considered as needed.

8.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study treatment taken by each subject, the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance.

A day within the study will be considered an "On-Therapy" day if the subject takes the assigned treatment (EBR/GZR± RBV) as noted in Section 5.2.

For a subject who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from the date of the first to the date of the last dose of study medication for that subject. Note, the date of the last dose of study medication would be the last scheduled day of treatment administration for subjects who completed the assigned treatment.

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

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

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

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 19.

Table 19 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-5172A (elbasvir/grazoprevir, EBR/GZR) 50 mg/100 mg	Tablet	Provided Centrally

All supplies indicated in Table 19 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 19 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open-label MK-5172A (EBR/GZR, 50 mg/100 mg) blister cards every 4 weeks. Each blister card will contain a 14 day supply. Two blister cards will support dosing requirements for a 28 day span between visits. At the day 1 visit 3 blister cards will be dispensed. The third blister card will cover the days between visits where the subject does not return for their visit on the 28th day. No kitting is required.

9.3 Clinical Supplies Disclosure

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

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 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 trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form 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 trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

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

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. 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 serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-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 trial reimbursed to the investigator by the Sponsor.

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent 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 trial 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 trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. 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 trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA 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 trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

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.

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

10.7 Publications

This trial 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 trial 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 trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on 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 Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures,

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, 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 trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial 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 must meet conditions 1, 2 and 3. Significant contributions to trial 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 trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending 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 trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 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."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing 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 Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens 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 trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent 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 trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

The Sponsor 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.

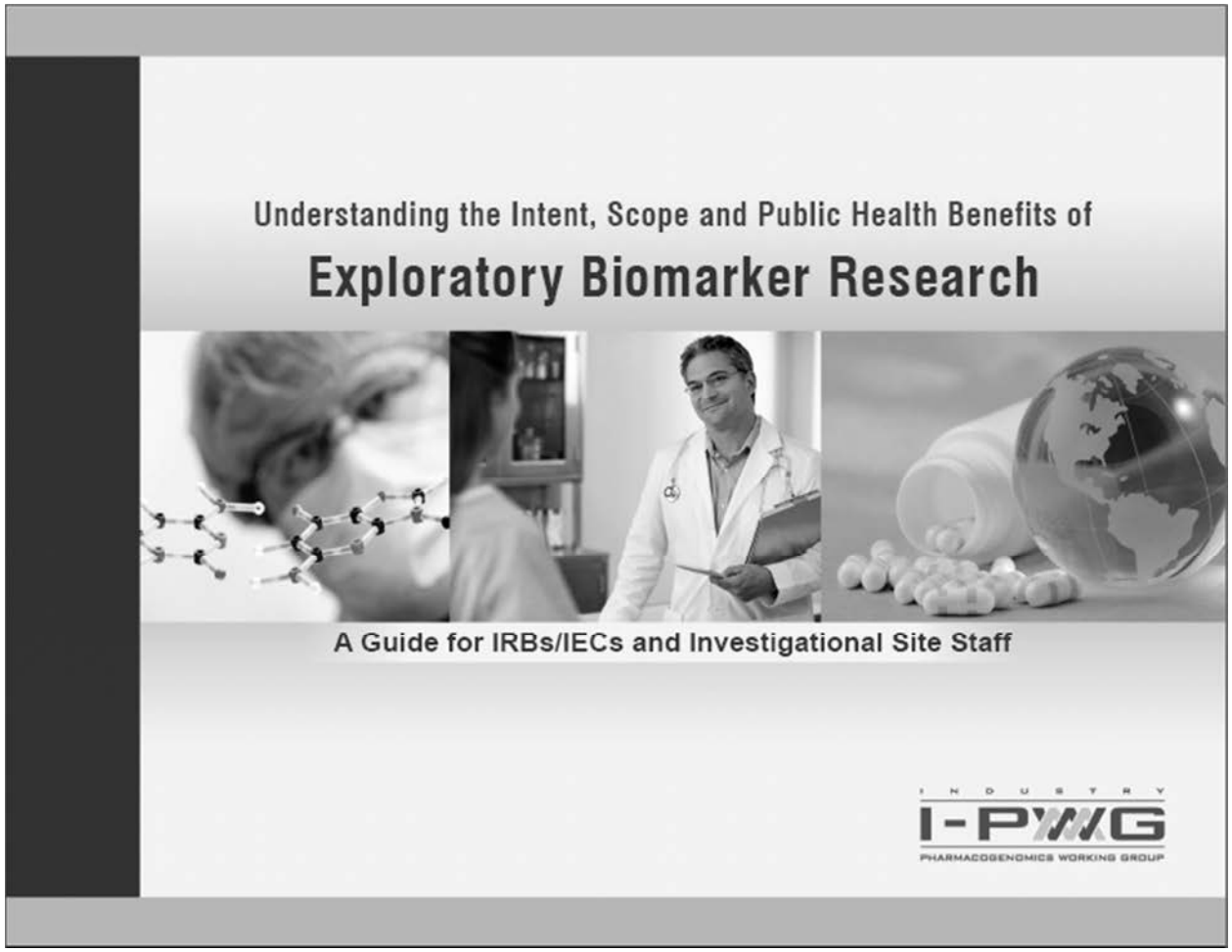
12. Questions

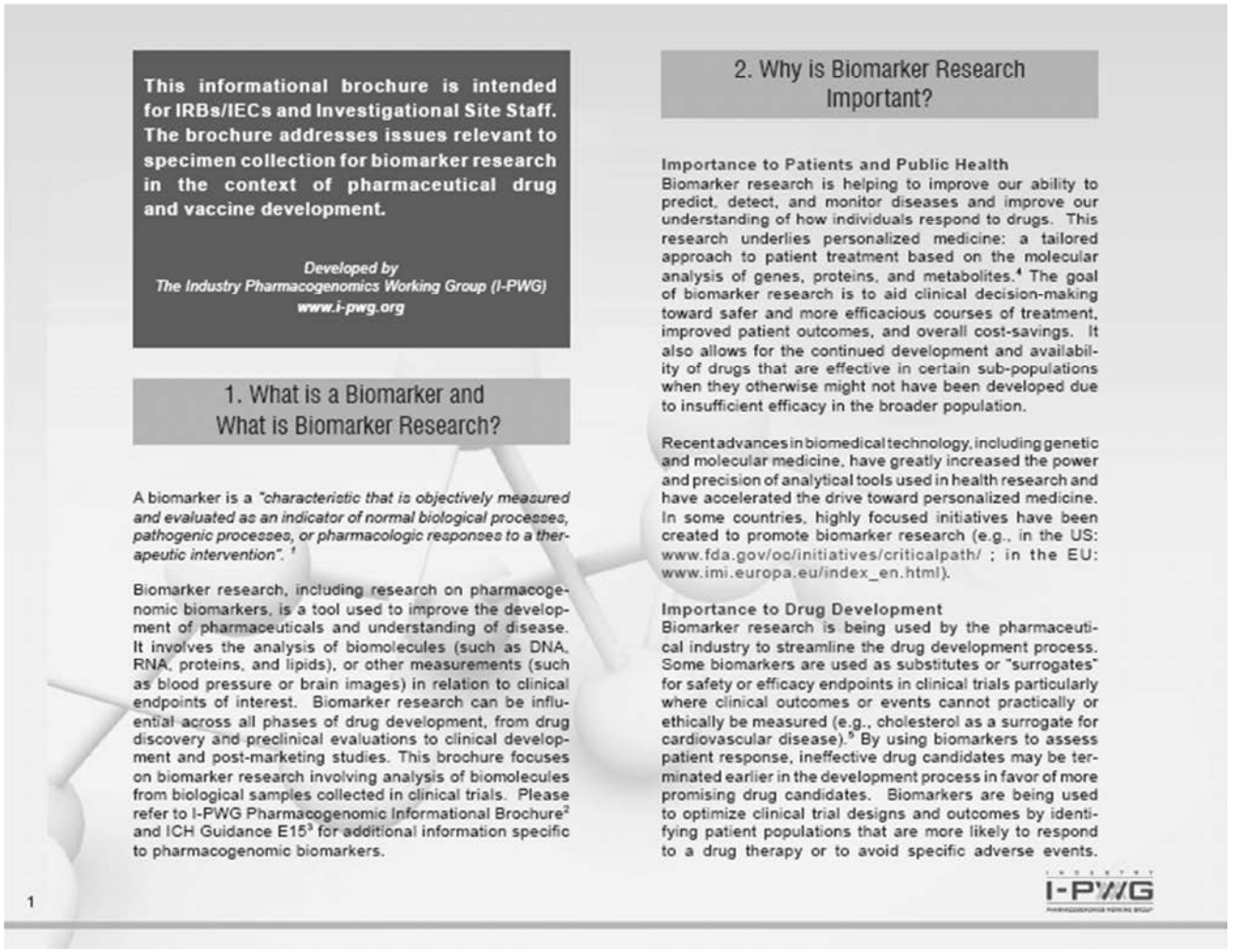
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

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

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development

Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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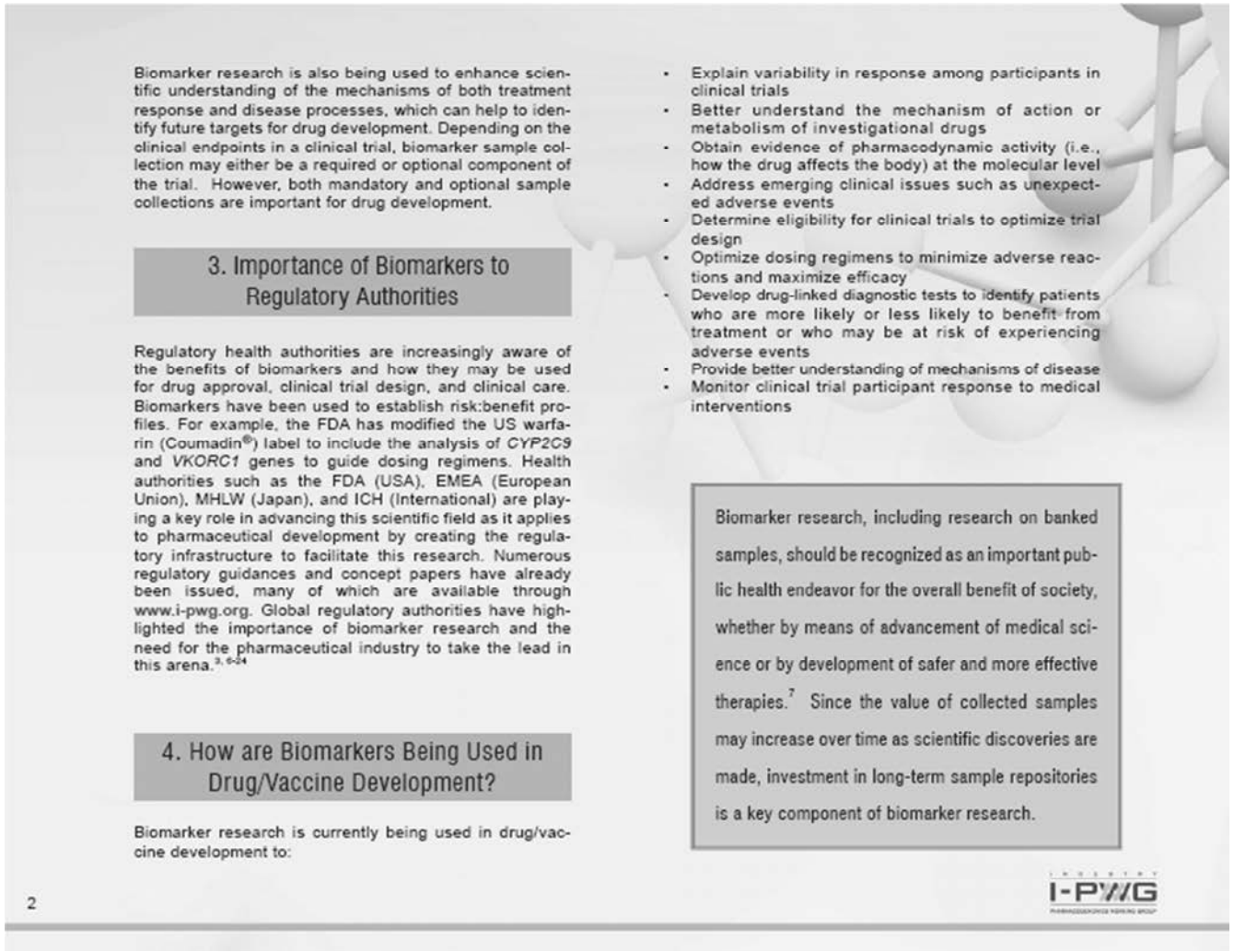
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health 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 by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3,6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
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 experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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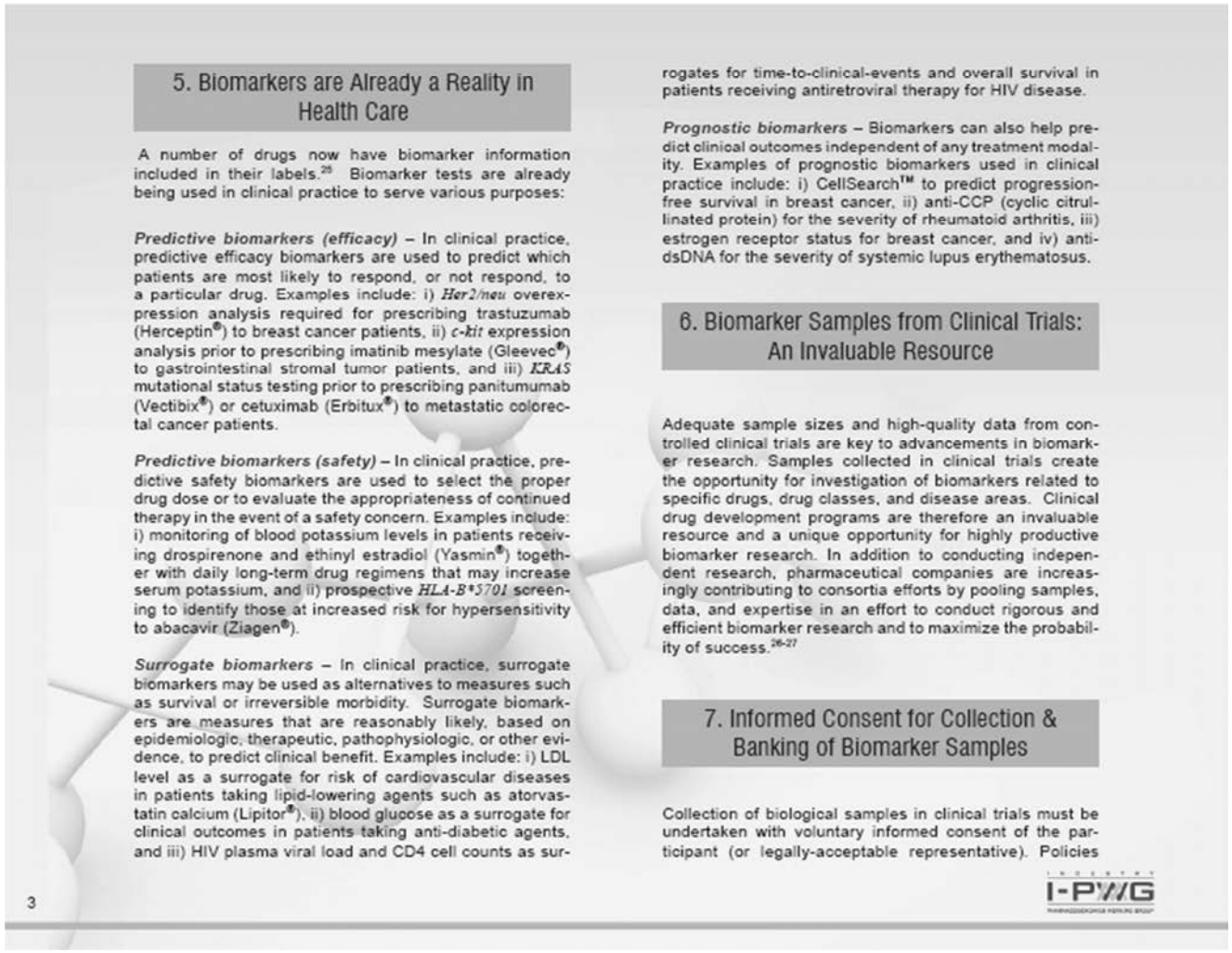

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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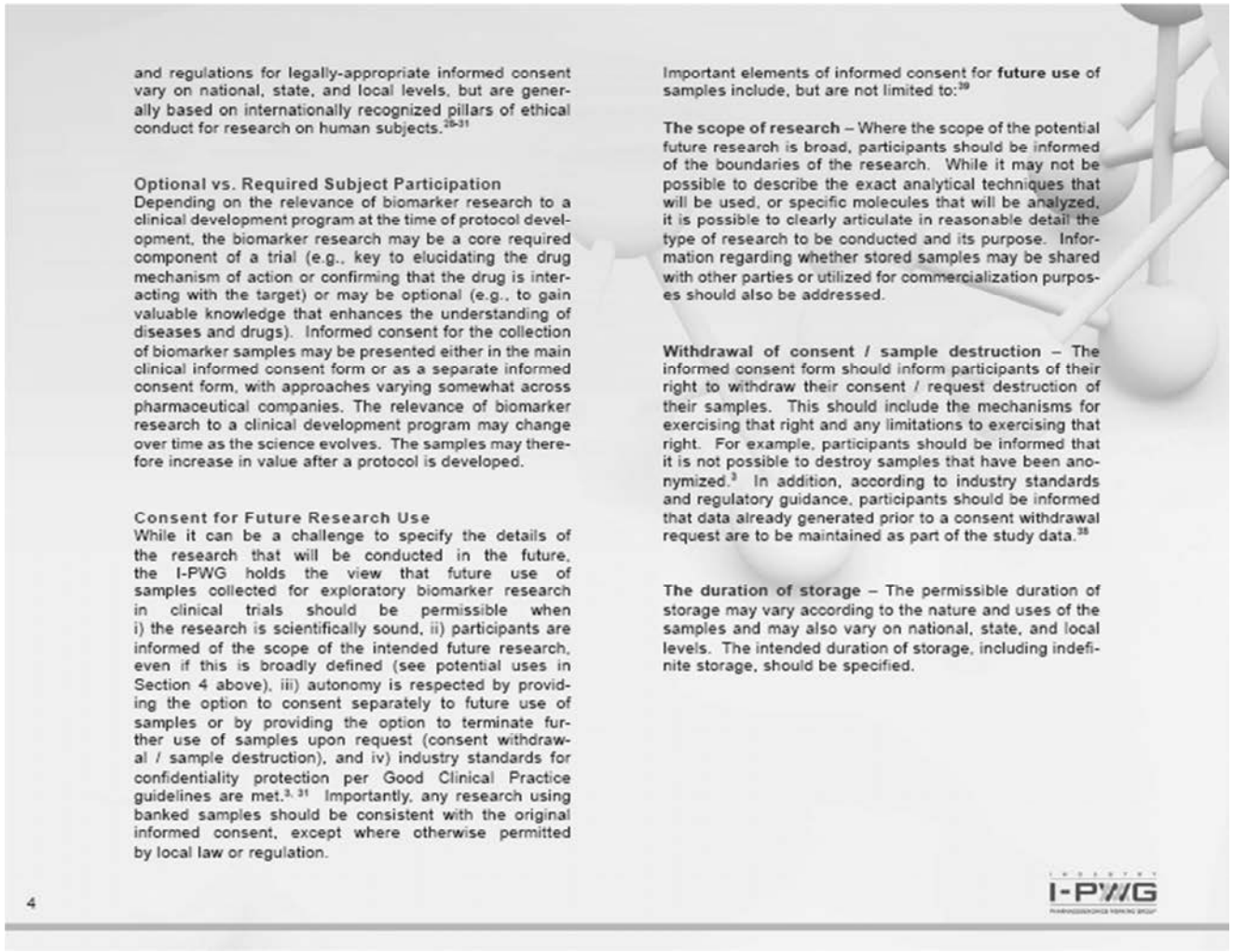

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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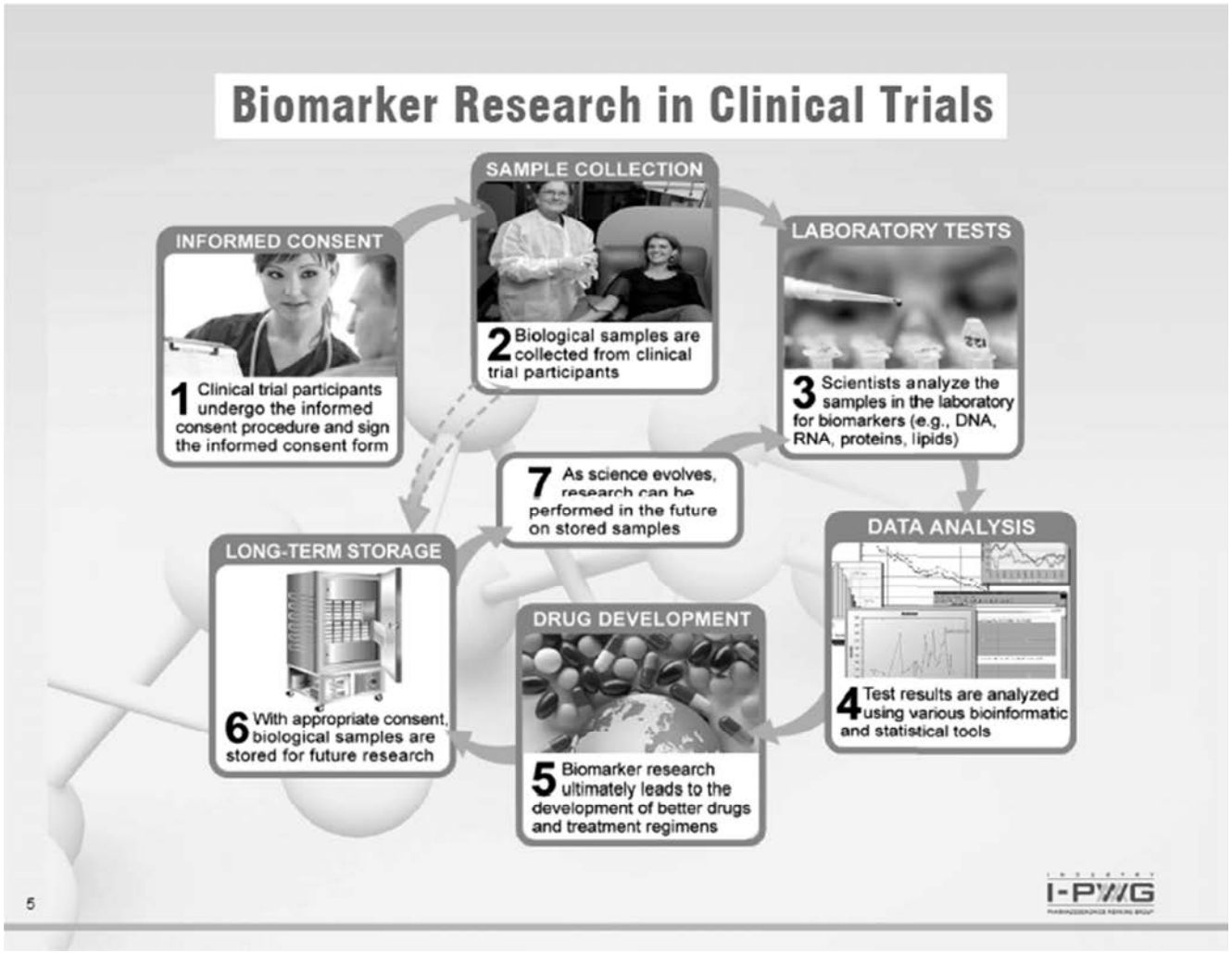
Biomarker Research in Clinical Trials
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
7 As science evolves, research can be performed in the future on stored samples
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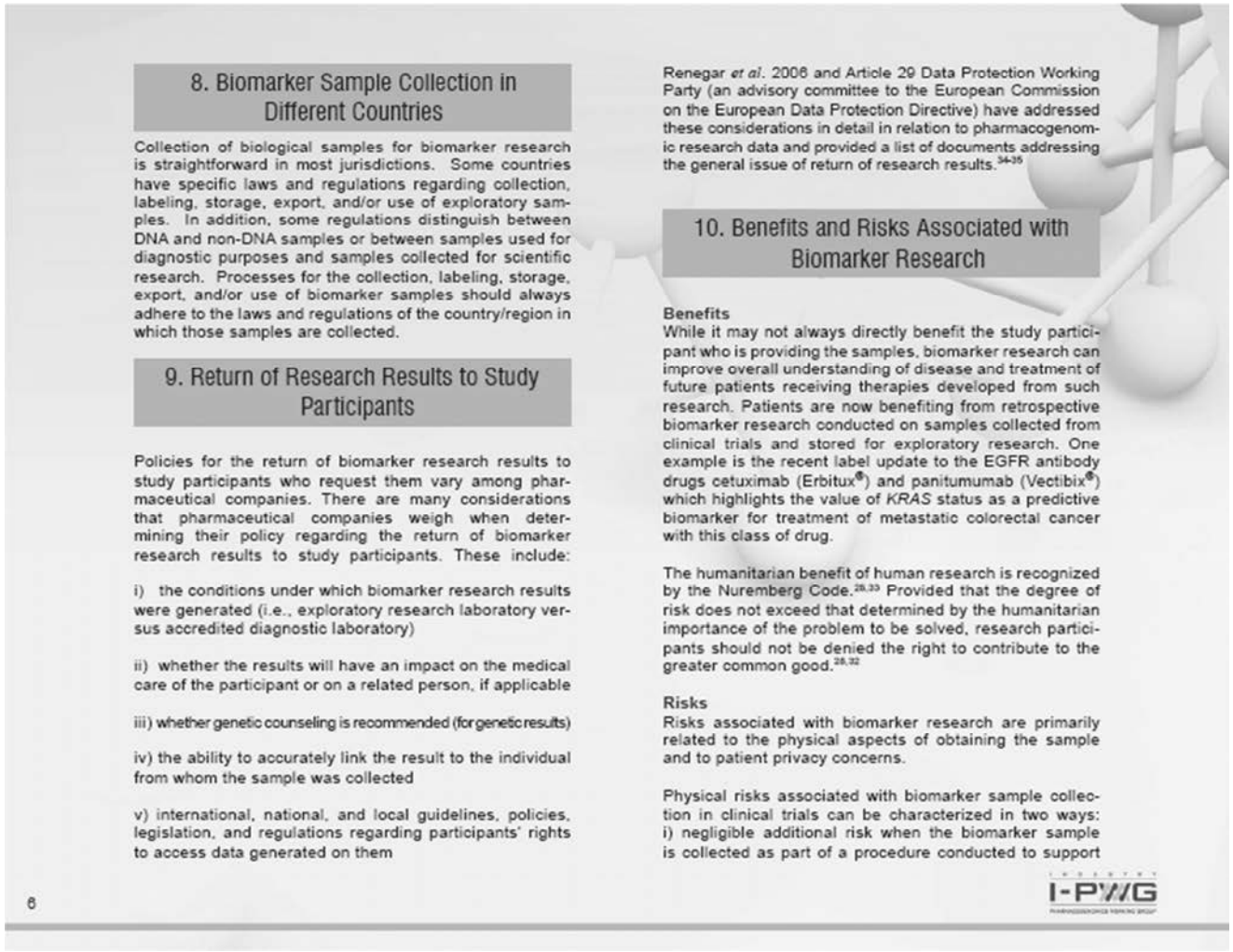

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic 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 pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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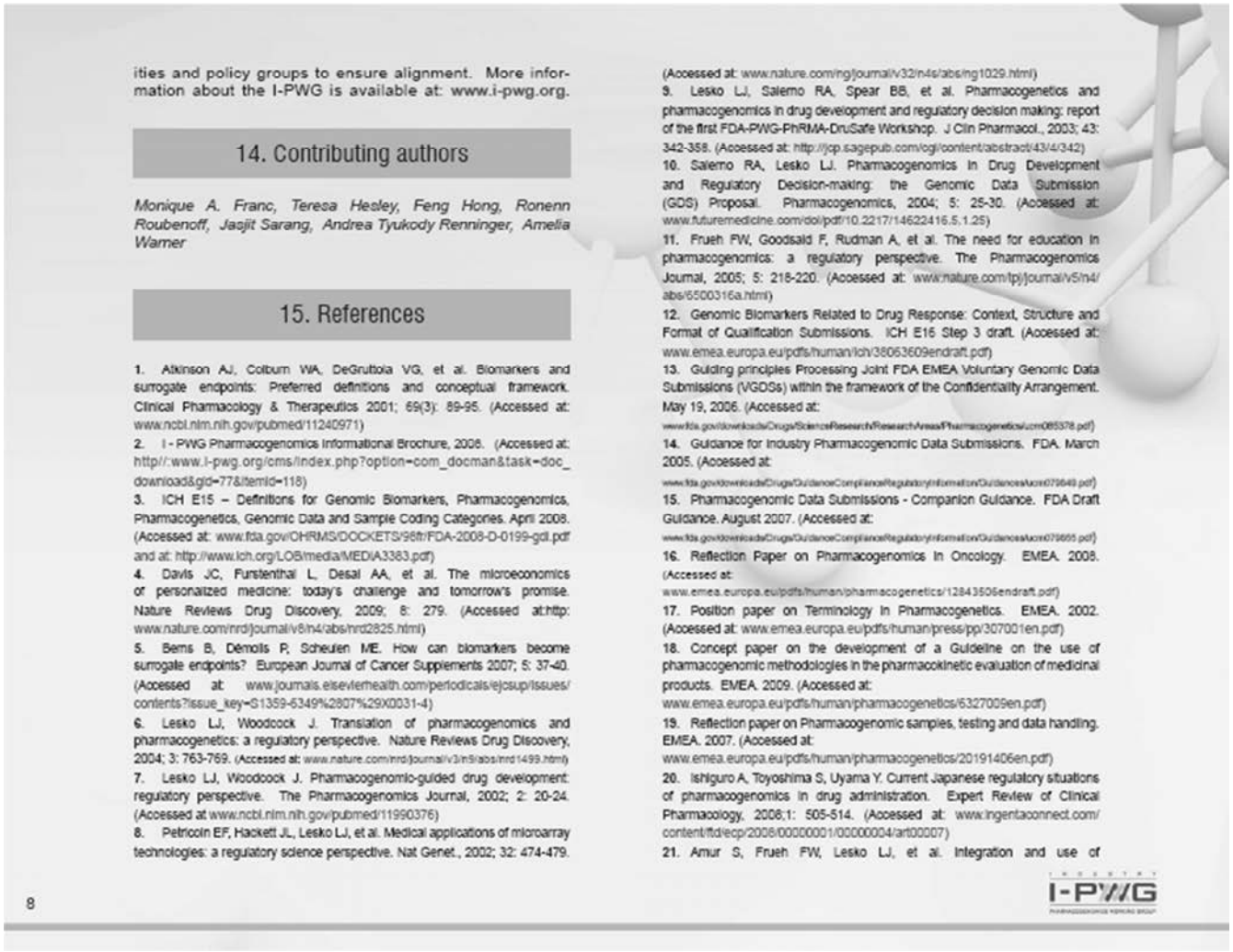

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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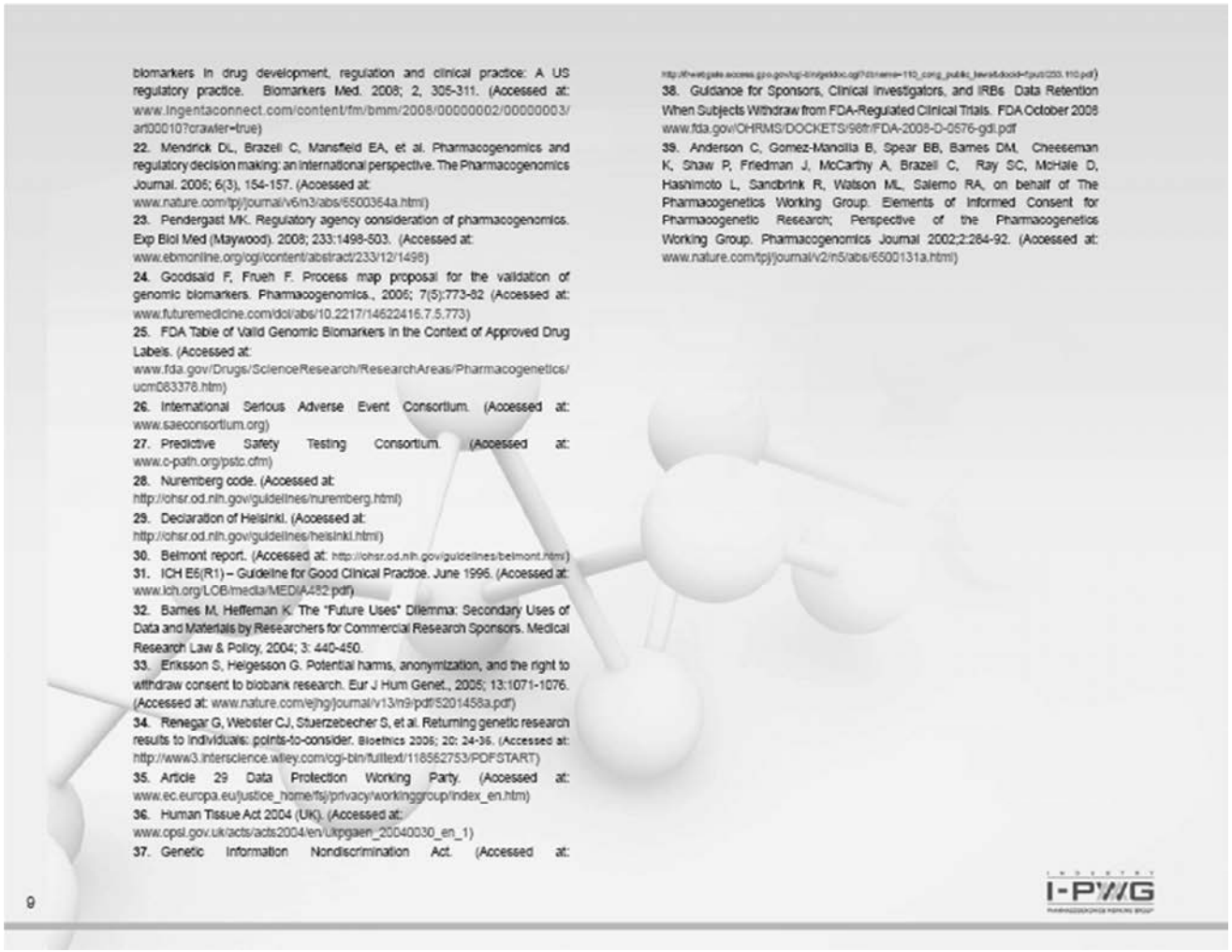

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www.i-pwg.org

12.4 List of Abbreviations and Definition of Terms

Term	Definition
AE	Adverse event
ART	Antiretroviral therapy
ASaT	All Subjects as Treated (population)
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EBR	Elbasvir
ECI	Events of Clinical Interest
eCRF	Electronic case report form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration, USA
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FDC	Fixed-dose combination
FU	Follow-up
FW	Follow-up Week
GCP	Good Clinical Practice
GCS	Global Clinical Supplies
GZR	Grazoprevir
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IL28B	Interleukin-28B (Interferon-lambda 3)
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Integrated web response system
LLOQ	Lower Limit of Quantification
mFAS	Modified full analysis set
NA, N/A	Not applicable
NI	Nucleotide-Mimetic NS5B Polymerase Inhibitor
NNI	Non-Nucleoside NS5B Polymerase Inhibitor
OBV	Ombitasvir
Peg-IFN	Pegylated Interferon alfa-2b
PGx	Pharmacogenomics
PI	Protease Inhibitor
RAV	Resistance-associated variants
RBC	Red Blood Cell
RBV	Ribavirin

Term	Definition
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SMD	Study Medication Diary
SOP	Standard Operating Procedure
SVR	Sustained Virologic Response
SVR_{12}	(Sustained Virologic Response 12 weeks after the end of all study therapy): The subject has HCV RNA <25 IU/mL (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 <25 IU/mL (either TD(u) or TND) 24 weeks after the end of all study therapy
TE	Treatment-experienced
TN	Treatment-naïve
TND	Target Not Detected (HCV RNA not detected)
TD (u)	Target detected but unquantifiable
TD (q)	Target Detected, quantifiable
TW	Treatment Week
US	United States

12.5 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

	Screening	Day 1	Week 4	Week 8	Week 12	FW 4	FW 12	FW 24	**Total Volume**
Test	Approximate Blood Volume (mL)								
Coagulation (PT, INR)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	36
HBV Evaluations (HBsAg, Anti-HBc, Anti-HBs, HBV DNA)[1]	10	10	10	10	10	10	10	10	80
HIV-1 Serology	6								6
Chemistry	10		10	10	10	10	10	10	80
Hematology	3	3	3	3	3	3	3	3	24
Follicle Stimulating Hormone (FSH)	2								2
HCV Genotype Determination	4								4
HCV Viral Resistance and biomarkers		6				6	6	6	24
HCV RNA	10	10	10	10	10	10	10	10	80
HIV RNA	6								6
CD4+ T-cell count	6								6
Blood for Genetic Analysis		8.5							8.5
Expected Total (mL) Main Study Population	61.5	52	37.5	37.5	37.5	43.5	43.5	43.5	356.5

Anti-HBc=hepatitis B core antibody; anti HBs=hepatitis B surface antibody; GT = genotype; HBsAg=hepatitis B surface antigen; HBV DNA=hepatitis B virus deoxyribonucleic acid; HCV=hepatitis C virus; HIV=Human immunodeficiency virus; INR=international normalized ratio; PT=prothrombin time.

[1] HBsAg, anti-HBc, and anti-HBs will be assessed at screening in all subjects. For all anti-HBc positive subjects, HBV DNA will also be assessed at screening, and both HBV DNA and HBsAg will be monitored during the trial.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial 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 serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). 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 trial 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	
TITLE	
SIGNATURE	
DATE SIGNED	