Official Protocol Title:	A Phase II, Open-Label Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-3682 + MK-8408 in Subjects with Chronic HCV Genotype 1, 2, 3, 4, 5 or 6 Infection
NCT number:	NCT02759315
Document Date:	26-Oct-2017

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One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

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

TITLE:

A Phase II, Open-Label Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-3682 + MK-8408 in Subjects with Chronic HCV Genotype 1, 2, 3, 4, 5 or 6 Infection

IND NUMBER: 123,749
EudraCT NUMBER: Not Applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
2.1; 6.0; 7.1.5.4; 7.1.5.6	Trial Design;Trial Flow Chart; Discontinued subjects continuing to be monitored in the trial; Long- Term Follow-up	The 3-year long term follow up (LTFU) portion of the study is being discontinued. Subjects that have enrolled in the LTFU will be discontinued via an unscheduled visit (telephone contact) and no further subjects will be enrolled in the LTFU period of the study.	These changes were made to discontinue the 3-year long-term follow-up period of the trial. Merck has made a strategic decision to discontinue the development of the investigational combination regimens MK-3682C (ruzasvir/uprifosbuvir) and MK-3682B (grazoprevir/ruzasvir/ uprifosbuvir). As a result, there is no need to obtain long-term follow-up on the persistence of resistance substitutions to ruzasvir or uprifosbuvir. The 3-year long-term follow-up period was observational; therefore, the removal of the 3-year long-term follow-up will have no impact on the safety of the study participants.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.2.3.3	Protocol-Specific Exceptions to Serious Adverse Event Reporting	The section heading was deleted	The section heading was deleted as there was no text content in this section

1.0 TRIAL SUMMARY

Abbreviated Title	MK-3682 + MK-8408 in Subjects with Chronic HCV GT1, 2, 3, 4, 5, or 6 Infection
Sponsor Product Identifiers	MK-3682 and MK-8408
Trial Phase	Phase II
Clinical Indication	Treatment of Hepatitis C virus infection
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Subjects will be assigned to receive MK-3682 (450mg) and MK-8408 (60mg) once daily for 12 weeks. Treatment-naïve and interferon-based treatment-experienced subjects without cirrhosis or with compensated cirrhosis (target ~25-30% compensated cirrhotics), and HIV co-infection may be enrolled. Subjects will be enrolled into one of six arms based on genotype: **Arm 1 (n=50):** GT1-infected subjects (35 GT1a and 15 GT1b) **Arm 2 (n=50):** GT2-infected subjects **Arm 3 (n=50):** GT3-infected subjects **Arm 4 (n~50):** GT4-infected subjects **Arm 5 (n~25):** GT5-infected subjects **Arm 6 (n~25):** GT6-infected subjects
Number of trial subjects	Approximately 250 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 68 weeks for the main study and up to a total of 200 weeks including long-term follow-up 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	Subjects will participate in the trial for approximately 42 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 45 days, each subject will receive assigned treatment for approximately 12 weeks. After the end of treatment, each subject will be followed for 24 weeks. Subjects who take at least 1 dose of study drug, experience virologic failure, complete Follow-up Week (FW) 24, AND consent to long-term follow-up will be followed for 3 years after last study dose, for a total trial participation of up to approximately 175 weeks.

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This study will evaluate a novel two-drug combination regimen to treat hepatitis C virus (HCV) infection of all genotypes (GTs). This is an open-label, multi-center trial in subjects with chronic HCV GT1, GT2, GT3, GT4, GT5 or GT6 infection. All subjects in this study will receive the same treatment regimen that consists of MK-3682 (450mg) + MK-8408 (60mg) co-administered concomitantly as separate medications once daily for 12 weeks. An estimated total of 250 subjects will be enrolled, with an overall target enrollment in six arms of 50 GT1, 50 GT2-, 50 GT3-, approximately 50 GT4-, approximately 25 GT5-, and approximately 25 GT6-infected subjects as displayed in Table 1. Subjects who have prior treatment experience with interferon (IFN)-based therapy may be enrolled, but subjects may not have previously received treatment with HCV direct-acting antiviral (DAA) therapy. Subjects may be HCV mono-infected or HCV/HIV-co-infected. HCV/HIV co-infected subjects and IFN-treatment-experienced subjects may be enrolled with no minimum number or caps.

Table 1 Treatment Regimen and Subject Characteristics

Treatment Regimen	Treatment Arm	Group Characteristics (N = 250)		
		Genotype (GT)	Target Enrollment	Target Cirrhotics
MK-3682 450 mg + MK-8408 60 mg for 12 weeks	1	GT1a	n = 35	n ~10
		GT1b	n = 15	n ~ 5
	2	GT2	n = 50	n ~15
	3	GT3	n = 50	n ~15
	4	GT4	n ~ 50	n ~15
	5	GT5	n ~ 25	N/A
	6	GT6	n ~ 25	N/A

If a total of ≥3 out of the first 10 subjects in the per-protocol (PP) population of the 12-week treatment arm experience virologic relapse by Follow-up Week 4 (FW4), the treatment duration of any remaining subjects of that genotype still on treatment in the 12-week arms will be extended to 16 weeks.

All subjects will be followed for 24 weeks after the end of treatment. Any subject who has taken at least one dose of study drug (either MK-3682 or MK-8408), experiences virologic failure, AND completes Follow-up Week (FW) 24 will be asked to extend follow-up for a total of 3 years after the end of treatment.

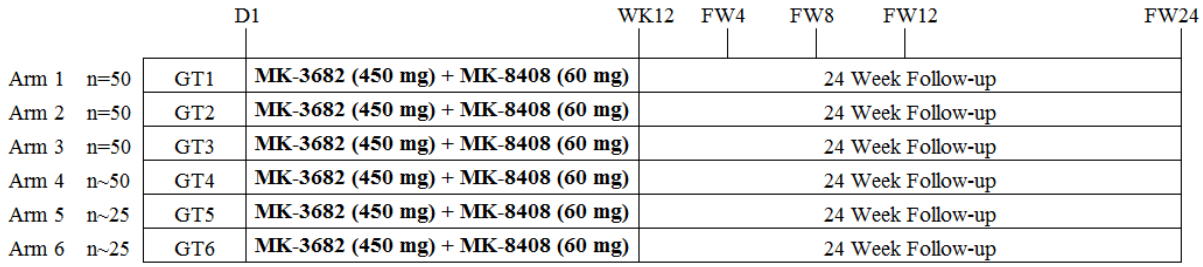
Amendment 04 implemented the discontinuation of the LTFU period of the trial. Subjects who already entered the LTFU period are to be discontinued (via an unscheduled visit). No further subjects will be entered into the LTFU period.

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.



Note: Subjects who take at least 1 dose of study drug, experience virologic failure, complete FW24, AND consent to long-term follow-up will be followed for a total of 3 years after the last study dose (Section 7.1.5).

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

This is an estimation study; there are no formal hypotheses.

In subjects infected with each HCV genotype:

1) **Objective:** To evaluate the efficacy of co-administered MK-3682 (450mg) + MK-8408 (60mg) following 12 weeks of treatment as assessed by the proportion of subjects achieving SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy), defined as HCV RNA < LLOQ 12 weeks after the end of all study therapy.
2) **Objective:** To evaluate the safety and tolerability of co-administered MK-3682 (450mg) + MK-8408 (60mg).

3.2 Secondary Objective(s) & Hypothesis(es)

Objectives will be evaluated separately for each HCV GT.

1) **Objective**: To evaluate the efficacy of co-administered MK-3682 (450mg) + MK-8408 (60mg) following 12 weeks of treatment, as assessed by the proportion of subjects achieving SVR_{24} (Sustained Virologic Response 24 weeks after the end of all study therapy), defined as HCV RNA < LLOQ 24 weeks after the end of all study therapy.
2) **Objective:** To evaluate the efficacy of 12 weeks of treatment with co-administered MK-3682 (450mg) + MK-8408 (60mg), as assessed by the proportion of subjects

who experience virologic failure (either on-treatment failure or relapse post-treatment) at Follow-up Week 12 among subjects who do not discontinue study for non-treatment-related (e.g., administrative) reasons.

3) **Objective:** To evaluate the effect of baseline resistance-associated variants (RAVs) in NS5A and/or NS5B on the efficacy of 12 weeks of treatment with co-administered MK-3682 (450mg) + MK-8408 (60mg), as assessed by the proportion of subjects with baseline RAVs achieving SVR_{12}.

3.3 Other Objectives (e.g., Tertiary, Exploratory, etc.)

1) **Objective:** To evaluate the pharmacokinetics (PK) of MK-3682 (including its metabolites) and MK-8408.
2) **Objective**: To evaluate the emergence of RAVs in NS5A and/or NS5B in subjects with virologic failure.
3) **Objective**: To explore the relationship between genetic variation, such as IL-28B genetic variation and clinical endpoints, to the treatment administered and mechanisms of disease. Variation across the human genome will be analyzed for association with clinical data collected in this study. See Sections 4.2.5.5, 4.2.5.6 and 12.2.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochures (IBs) for detailed background information on MK-3682 and MK-8408.

4.1.1 Pharmaceutical and Therapeutic Background

MK-3682 is an HCV NS5B polymerase nucleotide inhibitor (NI).

MK-8408 is an HCV NS5A replication complex inhibitor (NS5AI).

4.1.1.1 Overview

This study will evaluate a novel two-drug combination regimen to treat HCV infection of all genotypes. Of the 6 HCV genotypes (GTs), GT1 and GT3 are the most common and account for approximately 46% and 22% of all global infections, respectively. GT1 has a broad geographical distribution, being the most common genotype in most of North America, Northern and Western Europe, South America, Asia and Australia [1]. GT3 HCV infection is most prevalent in India, Pakistan, and Southeast Asia. GT2 infection is the third most common genotype worldwide and has a broad geographical distribution. GT4 infection is found predominantly in Africa and the Middle East [1], but is increasingly prevalent in France and Southern Europe due to increasing transmission through injection drug use [2]. Although GT5 and GT6 have a more limited geographic distribution than the other genotypes, they predominate in certain regions and represent an unmet medical need in those areas with GT5 and GT6 found mostly in sub-Saharan Africa and in Asia, respectively [1].

With the advent of oral DAAs, effective IFN and ribavirin (RBV)-free combination regimens are now available for subjects chronically infected with certain genotypes. However, some subgroups of subjects, particularly treatment-experienced, cirrhotic subjects, do not achieve optimal rates of sustained virologic response (SVR) with existing, approved 12-week regimens. In addition, the currently available dosing regimens are different for different HCV genotypes, with some regimens requiring prolonged treatment of up to 24 weeks with or without RBV, thus leading to complexity of treatment. Therefore, a regimen without the efficacy, safety, and convenience deficits of the existing regimens will be a substantial advance in the treatment of HCV infection. Because HCV is an RNA virus capable of substantial mutation in response to targeted antiviral agents, highly efficacious treatments for HCV infection require combinations of DAAs that simultaneously attack multiple points of the viral replication cycle. MK-3682 and MK-8408 are potent, once-daily antiviral agents that inhibit the HCV NS5B RNA polymerase and NS5A replication complex, respectively. This study will evaluate the efficacy and safety profile of a novel combination regimen of MK-3682 and MK-8408 that simultaneously targets two key points in the viral life-cycle.

The preclinical and clinical profiles of MK-3682 and MK-8408 demonstrate high potency against GT1-6 *in vitro*, supporting the use of this two-drug combination in this trial. MK-3682 is at least equipotent to sofosbuvir (SOF), an approved NI that anchors multiple current all-oral DAA therapies. In *in vitro* replicon studies, MK-8408 is more potent against multiple HCV genotypes and resistant variants compared with other NS5AI, such as the approved drugs ledipasvir (LDV), daclatasvir (DCV), ombitasvir (OMB) and elbasvir (EBR), and velpatasvir (VEL). Therefore, a regimen that combines MK-3682 and MK-8408 may be sufficient to result in high efficacy in clearing HCV infection of all genotypes. The rationale for the subject population, study design, doses of each of the compounds, and the duration of therapy are provided in subsequent sections.

4.1.1.2 Current Treatment of HCV

GT1: All oral, IFN-free regimens have demonstrated high degrees of efficacy in treating GT1–infected subjects. The highest efficacy rates have been observed in treatment-naïve patients. An approved 12-week regimen of the fixed-dose combination (FDC) of SOF/LDV resulted in SVR_{12} rates of 96% to 99% in treatment-naïve (TN), non-cirrhotic (NC) and 94% in cirrhotic (C) GT1-infected subjects [3, 4, 5, 6]. SOF/LDV also resulted in SVR_{12} rates of 94% in TE NC and C GT1-infected subjects [7]. An approved 12-week regimen of ombitasvir/paritaprevir/dasabuvir/ritonavir with RBV achieved SVR_{12} rates of 96% in TN, NC patients and 92% in cirrhotic GT1-infected subjects [8, 9, 10]. Without RBV, the corresponding SVR_{12} rate was 99.0% for GT1b and 90.2% for GT1a NC subjects [11]. Ombitasvir/paritaprevir/dasabuvir/ritonavir with RBV also achieved SVR_{12} rates of >95% in TE GT1-infected subjects [12]. An approved 12-week regimen of grazoprevir (GZR)/ EBR in TN, NC and cirrhotic GT1-infected subjects achieved SVR_{12} rates of 94.1% and 97.1%, respectively [13, 14], and SVR_{12} rates of 94.0% and 100.0% in TN NC and cirrhotic HIV co-infected GT1- and 4-infected subjects, respectively [14, 15]. In the ASTRAL-1 Phase 3 study, the investigational two-drug combination of SOF/VEL for 12 weeks in GT1-infected NC and C subjects with or without previous IFN-based treatment achieved an SVR_{12} of 98% to 99% (323/328) [16].

GT2: Current all-oral therapy for GT2 infection consists of a 12-week regimen of SOF/RBV. A 12-week regimen of SOF/RBV for TN patients with HCV GT2 infection was studied in 3 clinical trials: FISSION, POSITRON, and VALENCE [17, 18, 19, 20]. Across all 3 trials, 94% of subjects achieved SVR_{12}. Based on real-world data from Trio Health, lower response rates were seen in TN subjects with cirrhosis than in those without cirrhosis [21]. Longer treatment duration improves SVR in treatment-experienced subjects with cirrhosis [18]. In current treatment guidelines, longer duration of treatment is recommended in HCV GT2–infected subjects with cirrhosis [22, 23]. In the ASTRAL-1 and -2 Phase 3 studies, the investigational two-drug combination of SOF/VEL for 12 weeks in GT2-infected NC and cirrhotic subjects with or without previous IFN-based treatment achieved an SVR_{12} of 99-100% (104/104 in ASTRAL-1 and 133/134 in ASTRAL2) [16, 24].

GT3: In GT3-infected subjects, a 24-week regimen of SOF/RBV resulted in SVR_{12} rates of ~80-85%, but showed reduced efficacy in prior pegylated-INF+RBV (PR)-treatment failures and cirrhotics [20]. More recent IFN-free studies have shown improved efficacy with a 12-week regimen of SOF/DCV, but continue to show reduced efficacy in prior PR-treatment failures and cirrhotics. SOF/DCV for 12 weeks resulted in SVR_{12} rates of 98% and 58% in TN NC and C subjects, respectively, and in 92% and 69% of TE NC and C subjects, respectively [25, 26, 27, 28]. In the ASTRAL-3 Phase 3 study, the investigational two-drug combination of SOF/VEL for 12 weeks in GT3-infected NC and cirrhotic subjects achieved an SVR_{12} of 97% (191/197) and 91% (73/80), respectively [24]. In this study, the SVR_{12} was 97% (200/206) among those who were TN, 90% (67/71) among those who were treatment experienced, and 89% in subjects who had received previous treatment and who had evidence of cirrhosis.

GT4: A number of 12-week regimens have been demonstrated to be highly efficacious in GT4-infected subjects. Currently approved all-oral regimens for treatment of GT4 include SOF/LDV, SOF/DCV, paritaprevir/ritonavir/ombitasvir/ritonavir with RBV, and GZR/EBR. SOF/LDV for 12 weeks is approved in the United States (US) for non-cirrhotic and cirrhotic subjects, having achieved SVR_{12} rates of 93% (41/44) and 100% (8/8) in two studies [5]. SOF/LDV is approved in the European Union (EU) for 12 weeks in non-cirrhotic subjects and for 12 weeks with RBV or for 24 weeks without RBV for cirrhotic subjects [6]. SOF/DCV is approved in the EU for 12 weeks in non-cirrhotic subjects and for 24 weeks for cirrhotic subjects [28]. Paritaprevir/ritonavir/ombitasvir with RBV is approved in the EU and US for 12 weeks in non-cirrhotic subjects and in the EU for 24 weeks for cirrhotic subjects, based on the results of the PEARL-1 trial, in which treatment-naïve and treatment-experienced subjects treated for 12 weeks achieved SVR_{12} in 100% (42/42) and 100% (49/49) of cases, respectively [10, 29, 30]. A 12-week regimen of GZR/EBR achieved a 96% (54/56) SVR_{12} rate in GT4-infected subjects treated for 12 weeks [13, 15, 14, 31]. In the ASTRAL-1 Phase 3 study, the investigational combination regimen of SOF/VEL for 12 weeks in GT4-infected NC and cirrhotic subjects achieved an SVR_{12} of 100% (116/116) [16].

GT5: SOF/LDV is currently the only US-approved all-oral regimen for treatment of GT5. SOF/LDV was administered for 12 weeks to 41 treatment-naive (n=21) or previously-treated subjects (n=20) with GT5 infection, with or without cirrhosis. The overall SVR_{12} was 95% (39/41) [5, 32]. In the ASTRAL-1 Phase 3 study, the investigational combination of SOF/VEL for 12 weeks in GT5-infected NC and cirrhotic subjects achieved an SVR_{12} of 97% (34/35) [16].

GT6: SOF/LDV is currently the only US-approved all-oral regimen for treatment of GT6. SOF/LDV was administered for 12 weeks to 23 treatment-naive and 2 previously-treated subjects with GT6 infection, with or without cirrhosis. The overall SVR_{12} was 96% (24/25) [5, 33]. In the ASTRAL-1 Phase 3 study, the investigational combination of SOF/VEL for 12 weeks in GT6-infected NC and cirrhotic subjects achieved an SVR_{12} of 100% (41/41) [16].

4.1.2 Pre-clinical and Clinical Trials

4.1.2.1 Summary of Preclinical Data

MK-3682

MK-3682 is a nucleotide prodrug inhibitor of the HCV NS5B RNA-dependent RNA polymerase. The preclinical profile demonstrates that MK-3682 has high potency against genotypes 1-6 *in vitro*. The triphosphate of MK-3682, MK-3682-NTP, is a potent, pangenotypic inhibitor of HCV NS5B polymerase, with mean IC_{50} values of 0.144 ± 0.011 μM (GT1a), 0.238 ± 0.024 μM (GT1b), 0.250 ± 0.005 μM (GT2a), 0.156 ± 0.012 μM (GT3a), 0.149 ± 0.016 μM (GT4a), 0.233 ± 0.003 μM (GT5a) and 0.097 ± 0.006 μM (GT6a).

MK-3682 has low HCV replicon activity due to a lack of the activating enzyme CES-1 in human Huh-7 replicon cells. Antiviral activity was therefore assessed using a closely related surrogate prodrug which shares the same active nucleoside triphosphate moiety as MK-3682. The surrogate prodrug had moderate activity against HCV replicons and did not demonstrate cross-resistance to several known resistance mutations in NS3, NS5A, and NS5B with the exception of NS5B S282T. Resistance to the surrogate prodrug in the HCV replicon was low level and emerged slowly. The *in vitro* data implicate S282T as the primary mutation responsible for surrogate prodrug resistance. Overall, the pan-genotypic in vitro potency profile and the moderate potency shift against signature RAV S282T for MK-3682 is similar to those observed for sofosbuvir [34].

MK-3682 belongs to a class of uridine-based nucleotide analogs, like SOF, that have been well tolerated. Certain purine (guanosine and adenosine) based nucleotide analogs utilizing a different prodrug platform have shown mitochondrial toxicities and have had clinical safety findings including liver toxicity, cardiomyopathy and hematologic toxicity. Notably, BMS-986094 (INX-189), a guanosine analog, showed myocardial degeneration in preclinical species and cardiomyopathy/heart failure in clinical trials and was discontinued. The *in vitro* and *in vivo* preclinical data demonstrate that MK-3682 and its predominant circulating metabolite have limited potential for mitochondrial toxicities at the exposures observed in clinical settings.

Comprehensive preclinical evaluations of MK-3682 and its predominant circulating metabolite have been performed to characterize thoroughly the safety of this compound prior to the conduct of clinical studies. Results of the nonclinical safety program to date have demonstrated an acceptable safety profile which compares favorably to other NIs and supports the continued clinical development of MK-3682. MK-3682 exhibited little or no *in vitro* cytotoxicity in a large number of proliferating and non-proliferating human and mammalian cell lines, showed no mitochondrial effects in highly proliferating hepatic and non-hepatic cells and exerted no measurable cytotoxicity in human cardiomyocytes. The

toxicity potential of MK-3682 has also been well characterized in a battery of *in vitro* and i*n vivo* genetic toxicity studies, safety pharmacology studies, as well as 2-week, 1-month, 3-month, and 6-month repeat-dose oral toxicity studies in rats and monkeys. Collectively, the toxicity studies identified minimal findings that were not considered adverse and identified the liver and kidney as potential target organs. No observed adverse effect levels (NOAELs) in the rat and Cynomolgus monkey provide adequate margins of safety relative to anticipated human doses. In summary, preclinical assessments have established that MK-3682 has promising characteristics as a clinically effective agent and support the use of MK-3682 in the treatment of GT1- to GT6-infection in the present study. Please refer to the MK-3682 IB for more information on the preclinical background of MK-3682.

MK-8408

MK-8408 is a potent NS5A replication complex inhibitor. NS5A is a pleiotropic protein with important roles in both HCV RNA replication and modulation of host cell physiology. MK-8408 has *in vitro* activity against replicons from all genotypes tested (Table 2). It has broad genotype activity with an EC_{50} ≤10 pM against sub-genomic replicons from GTs 1-6. The in vitro potency profile of MK-8408 is comparable or better than other NS5A inhibitors, such as ledipasvir, EBR, and velpatasvir (Table 2). MK-8408 retains its potent activity in full-length infectious viruses from GT1a (H77Sv3) and GT2a (JFH-1), as well as against GT1a RAVs selected by previous NS5A inhibitors in the clinic (Table 3). Its potency is also not affected by signature RAVs from other HCV DAA classes. MK-8408 interacts synergistically with replicon-active analogues of MK-3682.

Table 2 Potency of MK-8408 versus First Generation NS5A Inhibitors in HCV GT1-GT6

	daclatasvir[c]	ledipasvir[d]	ombitasvir	velpatasvir	elbasvir	MK-8408
Genotype	**EC_{50} (pM)**					
1a (H77)	50	34	14	12	4	**1**
1b (con1)	9	4	5	15	3	**2**
2a (JFH1)	71	21000	12	9	3	**1**
2b_31M[a]	n/a	n/a	4.3	8	3000	**4**
3a	146	35000	19	12	20	**2**
4a[b]	12	110	1.7	9	3	**2**
5a[a]	33	150	3.2	75	1	**1**
6a[a]	n/a	120	366	130	3	**4**

[a] NS5A chimeric replicons from gt2b, gt5 & gt6 were constructed in the background of JFH-1.
[b] GT4a NS5A was in the con1 background. Full-length NS5A was evaluated.
[c] [35]
[d] [36]
[e] [37]
n/a = not available

Table 3 Potency of MK-8408 in Treatment-Emergent GT1a RAVs Selected by Approved NS5A Inhibitors in Transient Replication Assay

	ledipasvir		ombitasvir		elbasvir		MK-8408	
	EC_{50} (nM)	Fold Shift	EC_{50} (nM)	Fold Shift	EC_{50} (nM)	Fold Shift	EC_{50} (nM)	Fold Shift
GT1a_H77 (WT)	0.068	1	0.12	1	0.013	1	0.016	1
M28A	17.367	257	40.33	330	0.486	39	**0.016**	**1**
M28T	2	30	210.5	1724	0.212	17	**0.016**	**1**
M28V	**0.038**	**1**	7	55	**0.019**	**2**	**0.016**	**1**
Q30E	65	962	41	336	0.516	41	**0.019**	**1.2**
Q30H	7	102	1.0	8	**0.045**	**4**	**0.013**	**0.8**
Q30K	32	478	21	175	0.469	37	**0.016**	**1**
Q30L	0.695	10	**0.07**	**0.5**	**0.006**	**1**	**0.007**	**0.4**
Q30R	9.5	141	80.5	659	0.229	18	**0.02**	**1.2**
L31M	10	150	**0.25**	**2**	0.118	9	**0.018**	**1.1**
L31V	19	276	6	48	0.821	65	**0.076**	**4.7**
H58D	26	380	15	124	0.072	6	**0.017**	**1.1**
H58P	**0.098**	**1**	**0.12**	**1**	**0.012**	**1**	**0.014**	**0.9**
Y93C	18	266	76	622	0.187	15	**0.011**	**0.7**
Y93N	342	5067	1421	11637	6.767	539	0.09	5.6
Y93H	98	1451	1138	9319	3.25	259	**0.042**	**2.6**

MK-8408 is highly selective; a selectivity factor of $>10^6$ was determined when profiled against a panel of 116 proteins comprising enzymes, receptors, ion channels and transcription factors. MK-8408 is not cytotoxic up to 25 μM in replicon cells. The toxicity potential of MK-8408 has also been well characterized in a battery of *in vitro* and i*n vivo* genetic toxicity studies, safety pharmacology studies, as well as 2-week, 1-month, 3-month, 6-month, and 9-month repeat-dose oral toxicity studies in rats and/or dogs. Collectively, the toxicity studies identified minimal findings that were not considered adverse. NOAELs in the rat and dogs provide adequate margins of safety relative to anticipated human doses. A 1-month oral combination toxicity study in rats co-administered MK-3682 with MK-8408 has also been completed and demonstrated no findings considered to be adverse or of toxicological significance. In summary, preclinical assessments have established that MK-8408 has promising characteristics as a clinically effective agent and support the use of MK-8408 in the treatment of GT1- to GT6-infection in the present study. Please refer to the MK-8408 IB for more information on the preclinical studies with MK-8408.

4.1.2.2 Summary of Clinical Data

4.1.2.2.1 Phase 1 Studies

MK-3682 and MK-8408 are currently being evaluated in multiple ongoing Phase 1 trials. Please refer to the MK-3682 and MK-8408 IBs for more detailed information on the Phase 1 clinical studies with MK-3682 and MK-8408. A brief summary of the relevant Phase 1 results is provided below.

MK-3682

Single and multiple oral doses of MK-3682 have been well tolerated. To date, there have been no safety signals identified for MK-3682 single doses of up to 900 mg of the tablet formulation and total daily doses of up to 300 mg of the capsule formulation for 14 days in healthy volunteers, as well as up to 450mg of the tablet formulation once-daily for 7 days in HCV-infected subjects. At a total daily dose of 300 mg of the capsule formulation × 7 days, mean maximal HCV RNA reductions were approximately -4.2 and -4.3 log10 IU/mL in GT1 and GT2 or GT3 HCV-infected subjects, respectively. At a total daily dose of 450mg of the tablet formulation × 7 days, the mean maximal HCV RNA reduction was approximately -4.58 log10 IU/mL in GT1-infected subjects. The magnitudes of viral load (VL) decline at 450mg of the MK-3682 tablet formulation are comparable to what was observed in the sofosbuvir monotherapy proof-of-concept study [38]. The rationale for dose selection in the current protocol is discussed in Section 4.2.2.1.

MK-8408

Single and multiple oral doses of MK-8408 have been well tolerated. To date, there have been no safety signals identified at single doses up to 600 mg and multiple doses once-daily up to 100 mg for 10 days in healthy volunteers, as well as multiple doses up to 120 mg once-daily for 5 days in HCV-infected subjects. At a total daily dose of 60mg × 5 days, mean maximal HCV RNA reductions were at least -3 log10 reduction in VL from baseline in GT1, GT2, and GT3 HCV-infected subjects. The magnitudes of viral load decline with MK-8408 are comparable to what was observed with velpatasvir monotherapy proof-of-concept study [39]. The rationale for dose selection in the current protocol is discussed in Section 4.2.2.2.

4.1.2.2.2 Summary of Ongoing Phase 2 Clinical Trials

MK-3682 and MK-8408 are currently being evaluated in combination with MK-5172 (grazoprevir or GZR, an HCV NS3/4A protease inhibitor). GZR is approved in the US in combination with EBR, MK-8742, an HCV NS5A inhibitor, for the treatment of HCV infection genotypes 1 and 4 as EBR/GZR (Zepatier™). A FDC of MK-3682/GZR/MK-8408 (MK-3682B) is currently being evaluated in three ongoing Phase 2 trials (MK-3682 PN011, MK-3682 PN012, and MK-3682 PN021) in GT1-6-infected subjects for 8 to 24-week durations with or without RBV. A brief summary of the Phase 2 three-drug combination regimen studies containing MK-3682 and MK-8408 is provided.

MK-3682 PN011 and PN012

MK-3682 PN011 and PN012 are two ongoing Phase 2 two-part, randomized, dose-ranging, parallel-group, multicenter, open-label trials to evaluate the safety and efficacy of three-drug regimens in subjects with chronic HCV GT1-GT6 infection. Subjects with GT1 and GT2 are being enrolled in PN011; subjects with GT3-GT6 are being enrolled in PN012.

In Part A of these studies, 93 GT1 (46 GT1a, 47 GT1b), 61 GT2, and 86 GT3-infected treatment-naïve, non-cirrhotic subjects with chronic HCV infection were dosed once-daily for 8 weeks duration with one of 4 regimens including MK-3682 (300 mg or 450mg), GZR (100 mg), and either EBR (50 mg) or MK-8408 (60mg).

All regimens were highly efficacious in subjects infected with GT1. No subject experienced virologic breakthrough on therapy. Across treatment arms, 45/46 (98%) GT1a and 46/47 (98%) GT1b subjects achieved SVR_{12}. There was no observed impact of NS5A RAVs

(defined as any change from wild-type at 9 positions (24, 28, 30, 31, 32, 38, 58, 92, or 93)); 23% of subjects had baseline NS5A RAVs, and all achieved SVR_{12}. No treatment-emergent RAVs were observed.

In subjects infected with GT2, the MK-3682 (450mg)/GZR/MK-8408 regimen was highly effective (94%), but SVR rates were suboptimal among subjects who received the other regimens (60-71%). The MK-3682 (450mg)/GZR/MK-8408 regimen achieved SVR_{12} among 94% (15/16) of GT2-infected subjects, despite a high prevalence of baseline NS5A RAVs (defined as any change from wild-type at 9 positions (24, 28, 30, 31, 32, 38, 58, 92, or 93)) in 94% (15/16) subjects. No treatment-emergent RAVs were observed.

All regimens were highly efficacious in subjects infected with GT3. Overall, 38/43 (88%) of subjects who received EBR and 40/43 (93%) of subjects who received MK-8408 achieved SVR_{12}. The MK-3682 (300 or 450mg)/GZR/MK-8408 regimens achieved SVR_{12} among 93% (40/43) of GT3-infected subjects, despite baseline NS5A RAVs (defined as any change from wild-type at 10 positions (24, 28, 30, 31, 32, 38, 58, 62, 92, or 93)) in 47% (20/43) subjects. One of the 3 relapsers in these arms had a treatment-emergent NS5A RAV (Y93H) at the time of failure.

All 240 subjects completed the full 8 weeks of dosing. All regimens were generally well tolerated, and no cardiac or renal safety signals were identified. The frequency and severity of adverse events (AEs) were comparable among the four treatment groups. The most frequent study drug-related AEs were headache (23%), fatigue (20%), and nausea (13%). One subject (1/240, 0.4%) experienced an alanine aminotransferase (ALT) increase >5× the upper limit of normal (ULN) at TW8 with a pattern consistent with the late ALT increases observed in the Phase 2 and 3 GZR studies, which rapidly resolved off study drug. There were no drug-related serious adverse events (SAEs) and no subjects discontinued due to AEs. The results of Part A demonstrated that an 8-week regimen of MK-3682 (450mg)/GZR/MK-8408 was highly effective and well tolerated in GT1-, GT2-, and GT3-infected treatment-naïve, non-cirrhotic subjects, supporting the selection of this regimen from the four tested in Part A for further evaluation among a diverse population of HCV-infected subjects, including those with additional HCV GTs, cirrhosis, prior treatment, and HIV/HCV-co-infection.

In Part B of these studies, the combination regimen is being administered as FDC tablets (MK-3682B). Each MK-3682B tablet contains GZR (50 mg), MK-3682 (225 mg), and MK-8408 (30 mg), and is administered as two tablets once daily, for a total daily dose of 100 mg GZR, 450mg MK-3682, and 60mg MK-8408. Non-cirrhotic and cirrhotic, treatment-naïve and pegylated-IFN/RBV (PR) treatment-experienced, GT1-GT6 subjects with or without HIV co-infection have received MK-3682B with or without RBV for 8, 12, or 16 weeks of therapy, depending on the treatment arm.

A total of 603 GT1, 2, and 3 subjects were enrolled in Part B: 153 GT1-infected (82 GT1a, 71 GT1b) treatment naïve (TN) patients with or without compensated cirrhosis, 135 GT2 TN patients (99 non-cirrhotic, 36 cirrhotic), and 315 GT3-infected treatment-naïve or treatment experienced (PR) patients with or without compensated cirrhosis. All patients were treated with MK-3682B, with or without RBV, for 8, 12, or 16 weeks. Patients could be mono-infected or HIV co-infected. Enrollment is underway for subjects infected with genotypes 4, 5 and 6, but no results are yet available for these GTs.

Results to date are available for 126 GT1-infected patients who have reached at least FW4 (Table 4). All subjects had undetectable HCV RNA at the end of 8 or 12 weeks of treatment. Of 41 patients (19 GT1a, 22 GT1b) who received 8 weeks of therapy who have reached FW4, 100% (41/41) have achieved SVR_4. Fifteen subjects were cirrhotic (2 GT1a/13 GT1b). Of 85 patients (46 GT1a/39 GT1b) who received 12 weeks of therapy who have reached FW4, 100% (85/85) have achieved SVR_4. 38 subjects were cirrhotic (17 GT1a/21 GT1b).

Table 4 Preliminary results for PN011 Part B for 8 and 12 weeks of MK-3682B in GT1-infected Treatment-Naïve Subjects With and Without Cirrhosis

	Non-Cirrhotic† n/N (% SVR)	**Cirrhotic† n/N (% SVR)**	**Total† n/N (% SVR)**
GT1a 8 weeks	17/17 (100%)	2/2 (100%)	19/19 (100%)
GT1b 8 weeks	9/9 (100%)	13/13 (100%)	22/22 (100%)
GT1a 12 weeks	29/29 (100%)	17/17 (100%)	46/46 (100%)
GT1b 12 weeks	18/18 (100%)	21/21 (100%)	39/39 (100%)
Total	73/73 (100%)	53/53 (100%)	126/126 (100%)

† $SVR_{4/8/12}$ (last visit on record) in subjects with ≥4 weeks of post-therapy follow-up

Baseline next-generation sequencing (15% sensitivity threshold) is available for 92 subjects; 7.8% (4/51) GT1a and 26.8% (11/41) GT1b subjects had baseline NS5A RAVs at positions 30, 31, and 93.

Treatment was generally well tolerated, with no cardiac or renal safety signals seen. PPD The most frequent study drug-related adverse events in >5% of all patients in all study arms were fatigue, headache, and nausea. The results to date suggest that MK-3682B for 8 or 12 weeks is highly effective and well tolerated in GT1-infected treatment-naïve, non-cirrhotic, and cirrhotic patients.

To date, data are available for 117 GT2-infected subjects with ≥4 weeks of post-therapy follow-up (Table 5). Among all participants, 134/135 (99%) subjects had HCV RNA < the lower limit of quantitation (LLOQ) at the end of their assigned 8, 12, or 16 weeks of treatment. One cirrhotic subject who was randomized to 12 weeks of MK-3682B + RBV had an HCV RNA that was 279 at TW12, despite being < LLOQ since TW2; HCV RNA was subsequently undetectable at FW4 and FW8. Compensated cirrhotic subjects were randomized to 12 or 16 weeks of treatment. Of the 117 subjects who have reached at least FW4, 39/45 (87%) of those assigned to 8 weeks of treatment (with or without RBV) have achieved SVR_4+ and 72/72 (100%) of those assigned 12 weeks of treatment (with or without RBV) have achieved SVR_4+. Of note, SVR_4+ was achieved for 100% (40/40) cirrhotic subjects for whom data are available at this time. SVR_4+ rates are comparable between arms of the same duration with or without RBV.

Table 5 Preliminary results for PN011 Part B for 8, 12 and 16 weeks of MK-3682B with or without RBV in GT2-infected Treatment-Naïve Subjects With and Without Cirrhosis; % of Subjects Achieving SVR_4+ of Those Who Have Reached at least FW4

	Non-Cirrhotic† n/N (%SVR)	**Cirrhotic† n/N (%SVR)**	**Total† n/N (%SVR)**
GT2 8 weeks (n=16)	14/16 (88%)	--	14/16 (88%)
GT2 8 weeks w/RBV (n=31)	25/29 (86%)	--	25/29 (86%)
GT2 12 weeks (n=31NC; 15C)	31/31 (100%)	10/10 (100%)	41/41 (100%)
GT2 12 weeks w/RBV (n=16)	--	10/10 (100%)	10/10 (100%)
GT2 16 weeks (n=26)	--	21/21 (100%)	21/21 (100%)
† $SVR_{4/8/12}$ (last visit on record) in subjects with ≥4 weeks of post-therapy follow-up updated 5 June 2016			

In the 8-week arms, failures are associated with detection of baseline substitutions at NS5A amino acid 31. Such substitutions are associated with an approximately 4-fold reduction in the potency of MK-8408 *in vitro*. Baseline next-generation sequencing (15% sensitivity threshold) is currently available for 35 of the 47 subjects receiving 8 weeks of treatment +/- RBV; 43% (15/35) of subjects had NS5A L31M at baseline. SVR_4+ for subjects with baseline L31M is 73% (11/15); for subjects with baseline 31L, SVR_4+ is 95% (19/20). The results to date suggest that MK-3682B for 12 weeks is highly effective and well tolerated in GT2-infected treatment-naïve, non-cirrhotic and compensated cirrhotic subjects.

Results to date are available for 283 GT3-infected patients who have reached at least FW4 (Table 6). All subjects had undetectable HCV RNA at the end of their assigned 8, 12, or 16 weeks of treatment. Of the 283 patients (189 non-cirrhotic, 94 cirrhotic) who have reached FW4, 98% (276/283) have achieved SVR_4. SVR_4 rates are comparable between different durations of treatment, arms with and without RBV, and between non-cirrhotic and cirrhotic subjects and those with or without prior PR treatment-experience.

Table 6 Preliminary results for PN012 Part B for 8, 12 and 16 weeks of MK-3682B in GT3-infected Treatment-Naïve and Treatment-Experienced Subjects With and Without Cirrhosis; % of Subjects Achieving SVR_4+ of Those Who Have Reached FW4

Regimen	Non-Cirrhotic, TN† n/N (% SVR)	Non-Cirrhotic, TE† n/N (% SVR)	Cirrhotic, TN† n/N (% SVR)	Cirrhotic, TE† n/N (% SVR)	Total† n/N (% SVR)
8 weeks	15/16 (94%)	15/15 (100%)			30/31 (97%)
8 weeks, RBV	35/35 (100%)	13/14 (93%)			48/49 (98%)
12 weeks	34/35 (97%)	14/14 (100%)	13/14 (93%)	9/9 (100%)	70/72 (97%)
12 weeks, RBV	35/35 (100%)	13/14 (93%)	15/15 (100%)	9/9 (100%)	72/73 (99%)
16 weeks		10/11 (91%)	10/10 (100%)	17/17 (100%)	37/38 (97%)
16 weeks, RBV				19/20 (95%)	19/20 (95%)
Total	119/121 (98%)	65/68 (96%)	38/39 (97%)	54/55 (98%)	276/283 (98%)

† $SVR_{4/8/12}$ (last visit on record) in subjects with ≥4 weeks of post-therapy follow-up

Baseline next-generation sequencing (15% sensitivity threshold) is available for 145 subjects; 16% (23/124) GT3 subjects had baseline NS5A RAVs at positions 30, 31, and 93. SVR (last visit on record) for subjects without baseline RAVs at positions 30, 31, or 93 is 99% (121/122); for subjects with baseline RAVs, SVR_4+ is 20/23 (87%).

Overall, treatment was generally well tolerated in all arms of the study, with no cardiac or renal safety signals observed. Among all genotypes in the Phase 2 studies, there was one death; PPD, considered unrelated to study drug. The most frequent study drug-related adverse events in >5% of all patients in all study arms were fatigue, headache, and nausea. The results to date suggest that MK-3682B for 8, 12 or 16 weeks is highly effective and well-tolerated in GT3-infected treatment-naïve or treatment-experienced, non-cirrhotic and cirrhotic patients.

Part C of PN011 and PN012 is evaluating a retreatment regimen for subjects in Part A who failed therapy. GT1-, GT2-, and GT3-infected treatment-naïve, non-cirrhotic subjects who relapsed after 8 weeks of therapy with any of the 4 regimens in Part A were offered retreatment with 16 weeks of MK-3682B plus RBV. Twenty-four of 26 eligible patients were enrolled, 2 with GT1, 14 with GT2, and 8 with GT3 infection. At the time of relapse following initial therapy, NS5A RAVs were detected in 0% (0/2) GT1, 93% (13/14) GT2, and 88% (7/8) GT3 patients. NS3 RAVs were detected in 50% (1/2) GT1, 100% (14/14) GT2, and 100% (8/8) GT3 patients. NS5B RAVs were detected in 50% (1/2) GT1, 0% (0/14) GT2, and 0% (0/8) GT3 patients, and 88% (21/24) patients had RAVs in >1 class.

One GT2-infected patient withdrew after a single dose with AEs of vomiting and tachycardia. The remaining 23 patients completed the full 16 weeks of dosing.

All subjects had undetectable HCV RNA at the end of treatment. All 23 patients (2 GT1, 13 GT2, and 8 GT3) have reached at least FW4; 100% have achieved SVR_4. Treatment was generally well tolerated, and no cardiac or renal safety signals were identified. The most frequent study drug-related AEs in >10% of all patients were headache, fatigue, nausea, rash, pruritus, insomnia, decreased hemoglobin and cough. The study results to date suggest that a 16-week regimen of MK-3682B plus RBV is effective and well-tolerated in GT1, GT2, and GT3-infected TN, non-cirrhotic patients who had previously failed 8 weeks of treatment with a 3-drug regimen, despite a high prevalence of baseline NS3 and NS5A RAVs.

MK-3682 PN021

MK-3682 PN021 is an ongoing Phase 2 randomized, multicenter, open-label trial to evaluate the safety and efficacy of MK-3682B for 16 weeks with RBV or 24 weeks without RBV in non-cirrhotic and compensated cirrhotic subjects with GT1 infection who have failed a previous DAA regimen. A subsequent cohort will enroll GT3 patients. Ninety-four GT1 patients have been randomized in this trial (78 [83%] GT1a; 16 [17% GT1b]). Patients had failed >8 weeks of ledipasvir/sofosbuvir (LDV/SOF) (59 [63%]), ≤8 weeks of LDV/SOF (13 [14%]) or EBR/GZR (22 [23%]). Forty-two patients (45%) had cirrhosis. MK-3682B has been well-tolerated thus far. To date, all subjects have achieved undetectable HCV RNA on treatment. No post-dose efficacy results are currently available.

In summary, treatment with MK-3682B has been generally well tolerated in >800 subjects in Phase 2 trials, with no cardiac or renal safety signals seen. Among all genotypes in the Phase 2 studies, PPD The most frequent study drug-related adverse events in >5% of all patients in all study arms were fatigue, headache, and nausea.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for the Trial

Currently approved HCV IFN-free DAA regimens, such as SOF/LDV, ombitasvir/paritaprevir/dasabuvir/ritonavir+RBV, and EBR/GZR, have better efficacy, tolerability, and convenience than earlier therapies; however, they are not uniformly effective across the 6 HCV genotypes. The most effective regimens are for genotype 1 HCV, which accounts for approximately 46% of infections worldwide [1]. Genotypes 2 and 3 HCV, the next most common genotypes, were historically grouped together in treatment guidelines. However, recent studies have shown that infection with GT3, especially in subjects with cirrhosis, is more difficult to treat [24, 26, 27]. In addition, although GT5 and GT6 have a more limited geographic distribution than GT1-4, they predominate in certain regions of the world and represent an unmet medical need with limited clinical experience. In addition, even though several IFN-free combinations are now available for treatment of HCV, clinicians must still take into account the genotype and even the subtype, as well as patterns of antiviral resistance in the choice of a regimen. The development of a single, uniform, and pangenotypic regimen that will be safe and effective in all patient populations would

represent a substantial advance in the treatment of HCV infection by greatly simplifying treatment paradigms and reducing the need for pretreatment testing and on-treatment monitoring. The clinical potential of the combination of MK-3682 and MK-8408, both once-daily medications, is suggested by their non-overlapping viral targets, the pangenotypic in vitro potencies of both MK-3682 and MK-8408, the proven success of other HCV NIs in combination with other NS5A inhibitors, and the high efficacy rates from the investigational three-drug regimen containing MK-3682, MK-8408, and GZR.

4.2.1.2 Rationale for the Selected Subject Population

The rationale for the patient populations selected for this trial is as follows:

- **Genotypes:** The efficacy of the two-drug regimen in HCV-infected subjects of all genotypes will be evaluated to allow for an initial assessment of the two-drug combination regimen of MK-3682 and MK-8408 as a pangenotypic therapy for HCV. The preclinical profiles of MK-3682 and MK-8408 demonstrate high potency against GT1-6 *in vitro*. In addition, the preliminary data from Phase 2 studies of MK-3682/GZR/MK-8408 demonstrate excellent tolerability and very high efficacy of this three-drug regimen when administered for 8 weeks or for 12 weeks in GT1- and GT3-infected subjects (see Section 4.1.2.2.2, above). In GT2-infected subjects there was excellent tolerability and the 12-week arm has had very high efficacy (100%), while the 8-week arm has shown sub-optimal efficacy (87%). Taken together, these data support the clinical evaluation of the combination of MK-3682 and MK-8408 as a pangenotypic therapy for HCV as a 12-week regimen in GTs 1-6.
- **Treatment-Naïve:** Treatment-naïve subjects who have never received medical therapy for HCV and have no evidence of cirrhosis represents the largest proportion of the HCV-infected population worldwide. Historically, these subjects have had a high response rate to HCV DAA therapies.
- **Treatment-Experienced Subjects**: This study will also include subjects who have previously failed treatment with IFN-based therapies, because subjects who have failed prior IFN-based treatment are among the populations at highest need for effective HCV treatments. Although the efficacy rates in IFN-based TE populations have historically been lower than in TN, more recent IFN-free DAA therapies combining highly potent drugs have demonstrated high rates of SVR_{12} in TE subjects that are comparable to those achieved in TN [4, 7, 12, 16, 18, 24, 40]. Given the comparable SVR_{12} rates observed following some all-oral DAA regimens in TE and TN subjects, TE subjects will be permitted to enroll in this study. As stated in Sections 4.2.1.3 and 8.9.1, this study includes duration modification rules to limit the potential for subjects to be at risk for virologic failure. Subjects who have failed prior DAA regimens will not be included in this study to allow further evaluation of this two-drug regimen to better understand the ability of this regimen to effectively treat subjects with baseline resistant variants in the context of this study before proceeding to further studies to evaluate the ability of the two-drug regimen to treat prior DAA failures.

- **Non-Cirrhotic Subjects**: Non-cirrhotic subjects represent a large proportion of the HCV-infected population worldwide. Historically, these subjects have had a high response rate to HCV DAA therapies.
- **Compensated Cirrhotic Subjects:** Subjects with cirrhosis who are at increased risk for progression to decompensated cirrhosis and liver complications are one of the more challenging groups in need of new therapeutic approaches. Although the efficacy rates in cirrhotic populations have historically been lower than in non-cirrhotics, requiring longer treatment durations or the addition of RBV to achieve equivalent SVR rates, more recent IFN-free DAA therapies combining highly potent drugs have demonstrated rates of SVR_{12} in compensated cirrhotic subjects that are comparable with those achieved in non-cirrhotic subjects [13, 16, 24, 40]. Most recently, the ASTRAL-1 Phase 3 study of SOF/VEL demonstrated 100% SVR in 5/5 GT5- and 6/6 GT6-infected cirrhotic subjects [16]. Given the comparable SVR_{12} rates observed following 12 weeks of all-oral IFN-free DAA regimens, including the 3-drug regimen of MK-3682/GZR/MK-8408 in non-cirrhotic and compensated cirrhotic subjects, subjects with compensated cirrhosis will be permitted to enroll in this study. In addition, as stated in Sections 4.2.1.3, 5.3 and 8.9.1, this study includes limitations on the number of cirrhotics, stopping rules, and duration modification rules to limit the potential for subjects to be at risk for virologic failure. Subjects with advanced or decompensated cirrhosis will not be included in this study.
- **HIV Co-infected Subjects:** HIV co-infected subjects are included in this trial, since HCV infection is a leading cause of morbidity and mortality among those with HIV-1 [41]. Compared to the general population, the overall prevalence of HCV infection is higher among those infected with HIV-1. In fact, one-fourth to one-third of subjects infected with HIV in the US and Europe are co-infected with HCV [42]. Compared to subjects infected with HCV alone, HIV/HCV co-infected subjects have higher baseline HCV VLs and more rapid progression of liver disease, including more rapid hepatic fibrosis as well as an increased risk of cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Subjects with HIV/HCV co-infection are also more susceptible to developing anemia, and they may have more rapid progression to acquired immunodeficiency syndrome (AIDS) and AIDS-related death [31]. Recent DAA therapies have demonstrated rates of SVR_{12} that are comparable with those achieved in HCV disease-matched mono-infected subjects. In particular, HIV subjects co-infected with HCV GT1- or GT4 had similarly high efficacy following EBR/GZR therapy in Phase 3 studies compared to those who were not HIV-infected [15]. Given the comparable SVR_{12} rates observed following all-oral IFN-free DAA regimens in mono-infected and co-infected subjects, HIV/HCV co-infected subjects will be permitted to enroll in this study.

4.2.1.3 Rationale for Study Design

The pangenotypic preclinical profiles of MK-3682 and MK-8408, as well as the preliminary results from the three-drug, 8- and 12-week regimens of MK-3682/GZR/MK-8408 in GT1, GT2 and GT3 support the preliminary evaluation of the safety and efficacy of 12 weeks of MK-3682+MK-8408 in treatment-naïve or prior IFN-based treatment experienced, non-cirrhotic and compensated cirrhotic GT1-, GT2-, GT3-, GT4-, GT-5, and GT-6-infected

subjects. A treatment duration of 12-weeks for all genotypes using the MK-3682+MK-8408 combination in this study is supported by the equipotent or superior *in vitro* potency profiles of MK-3682 and MK-8408 (Table 2 and Table 3) compared to other compounds of the same classes, such as the approved NI/NS5A SOF/LDV or SOF/VEL, that have demonstrated high efficacy rates against GT1-6 after 12 weeks of treatment as two-drug IFN-free DAA regimens. RBV is not proposed to be evaluated in this study given the high efficacy rates observed with other two-drug all-oral DAA regimens without RBV, such as SOF/LDV and SOF/VEL, and the equipotent or superior *in vitro* potency profiles of MK-3682 and MK-8408 compared to these regimens.

Since this is an estimation study, no comparator or placebo is used. No statistical comparisons are planned for efficacy and safety data. The target number of GT1-, GT2-, GT3-, and GT4-infected subjects is specified in order to provide sufficient confidence of the estimated treatment response rate in these genotypes, since they are the most prevalent genotypes globally. Since subjects with genotypes 5 and 6 are uncommon outside of certain geographic areas, the study will enroll approximately a targeted number of subjects with the assumption that full enrollment of these genotypes may not be reached.

If a total of ≥3 out of the first 10 subjects in the per-protocol population of the 12 week arms experience virologic relapse by FW4, all subjects already enrolled and on treatment for that GT will have their treatment duration extended to 16 weeks. This treatment duration modification rule was chosen in order to stop a regimen that had a reasonable probability of being insufficiently effective (in this case because of insufficient duration), while not prematurely discontinuing a regimen that could be successful. This choice was based on the following calculations to estimate the probability of observing a given number of subjects with virologic failure rates assuming a range of true SVR rates. Assuming a protocol violation rate of 10%, the PP population will include approximately 9 subjects out of the first ten of each genotype. The probability of observing 3 or more subjects with virologic failure out of 9 subjects per arm is 53.7%, 39.9%, 26.2%, 14.1%, and 5.3% assuming the true SVR rates of 70, 75, 80, 85, and 90%, respectively. Detailed information on these calculations is in Section 8.7. This modification rule provides an approximately 40% probability of extending treatment duration of a given genotype in the study for a true SVR rate of 75% or less, but is unlikely to extend the treatment duration if the SVR rate is 90% or higher (which is the SVR rate expected from a competitive regimen).

Patients who fail the MK-3682+MK-8408 regimen will be followed long-term, as described in Sec. 7.1.5.6. No rescue medications are included in this trial because it is not clear which rescue regimen would be optimal for patients who fail MK-3682+MK-8408. Subjects who experience virologic failure will be considered for future therapy once data are available to guide selection of rescue regimens. The composition and duration of future retreatment will be informed not only by the efficacy and RAVs observed at baseline and at failure in this study, but also from results from ongoing Phase 2 studies of MK-3682B. The efficacy of MK-3682B in cirrhotic and non-cirrhotic patients at different durations in GT1-6 is being evaluated in Part B of MK-3682 PN011 and PN012. In addition, results from Part C of MK-3682 PN011 and PN012, in which subjects who failed 8-week regimens of MK-3682+ GZR + either MK-8408 or EBR, are being retreated with a regimen consisting of 16 weeks of MK-3682B plus RBV, may provide insights into the optimal treatment for these patients. MK-3682 PN021 is evaluating retreatment of GT1-infected patients who have previously failed

all-oral DAA regimens with regimens of 16 weeks of MK-3682B plus RBV or 24 weeks of MK-3682B without RBV. The role of RAVs in virologic failures in these studies will be analyzed and results from other retreatment studies using currently available therapies will be considered in evaluating the optimal retreatment regimen for potential subjects who fail treatment in this study.

Additional stopping rules are described in Section 5.11.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The regimen selected for administration in this trial is 450mg of MK-3682 + 60mg of MK-8408 administered concomitantly once daily as separate medications.

4.2.2.1 Dose Selection for MK-3682

The 450mg dose of MK-3682 was chosen for this study based on the dose-response analysis generated by monotherapy data from MK-3682 PN001. This analysis suggests that the 450mg dose of the tablet formulation is on the plateau of the dose-response curve and would provide a greater margin to loss of efficacy than would the 300mg of the tablet formulation, while still maintaining margins to preclinical safety exposures. Although the 300mg and 450mg MK-3682 dose arms had comparable efficacy in GT3-infected subjects in PN012 Part A (SVR_{12} of 39/42 (93%) and 39/44 (89%), respectively), a slightly higher efficacy was observed in in GT2-infected subjects in MK-3682 PN011 Part A who were on the 450mg dose of MK-3682, with an SVR_{12} rate of 77% (24/31) versus 70% (21/30) on the 300 mg dose. The highest efficacy in GT2-infected subjects was observed in the MK-3682 (450mg)/GZR/MK-8408 arm with an SVR_{12} rate of 94% (15/16), supporting the selection of this regimen for this study. In addition, the 450mg dose of MK-3682 has demonstrated an acceptable safety profile in Part A of MK-3682B PN011 and PN012 when co-administered with GZR and MK-8408 or MK-8742.

4.2.2.2 Dose Selection for MK-8408

The 60mg dose of MK-8408 was chosen for the MK-3682B FDC regimen based on the available safety, tolerability, and pharmacokinetic data from the single and multiple dose and drug-interaction studies in healthy volunteers and the pharmacokinetic, pharmacodynamic (PD) and safety profiles of MK-8408 in HCV infected subjects. Preliminary pharmacodynamic data from PN003 are available for doses up to 120 mg in HCV GT3 subjects and demonstrate that following once daily fasted dosing of 10, 30, 60, and 120 mg MK-8408 for 5 days, the mean maximum reduction in HCV VL was -2.83, -3.03, -3.35 and -1.75 log10 IU/mL, respectively. The anomalous fall in VL decline at 120 mg dose of MK-8408 was explained by sequencing of the HCV subjects' isolates that revealed that all 3 subjects in this panel had either baseline or treatment-emergent resistance-associated variant viruses. One subject had the resistant variants S62L/Y93H at baseline and following treatment; this subject had a maximal VL reduction of -0.34 log 10 IU/mL. One subject had no detectable RAVs at baseline but had both S62L and Y93H emerge during treatment; this subject had a -1.85log10 IU/mL VL reduction. The third subject had A30K at baseline with emergence of Y93H/Y during treatment; this subject had a -3.06log10 IU/mL VL reduction. These VL results demonstrate that 30 mg and 60mg of MK-8408 are associated with a substantial and rapid initial VL decline of GT3, but that MK-8408 may not exhibit full

efficacy against some GT3 RAVs in the setting of monotherapy administration. Following a single dose of 60mg MK-8408 once-daily × 5 days the mean maximum reduction in HCV VL in GT1a subjects was -3.86 log10 IU/mL, and the mean maximum reduction in HCV VL in GT2b subjects was -3.62 log10 IU/mL. For detailed information, please refer to the MK-8408 IB.

The fit-for-purpose capsule formulation of MK-8408 demonstrates a moderate negative food effect, with a 50% decrease in C24hr when co-administered with a high fat meal. As such, in this study, subjects will be instructed to take study drugs on an empty stomach after an overnight fast, at least 1 hour before the morning meal. Study drugs should be taken with water, but without food. Drug-drug interaction studies with MK-3682 and MK-8408 (MK-3682 PN007 and MK-3682 PN008) demonstrated no clinically significant drug interactions, thus supporting the coadministration of these drugs without need for dose adjustment.

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 SVR, has been associated with improved outcomes in subjects with chronic HCV 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 as well as improve survival [43].

The primary evaluation of efficacy in this trial is based on SVR_{12}, the same endpoint used for all investigational and approved DAAs (e.g., simeprevir, SOF). Since a high degree of concordance has been observed between SVR_{12} and SVR_{24} [44], SVR_{12} is now being used as the primary endpoint for registration of DAAs. A secondary evaluation of efficacy is based on SVR_{24} (Sustained Virologic Response 24 weeks after the end of all study therapy), and for this study this will be a secondary endpoint [45].

4.2.3.1.1 Measurement of HCV RNA

HCV-RNA levels in plasma will be measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from each subject at various time points prior to, during, and after dosing, as indicated in the Study Flow Chart (Section 6.0). Samples are collected and processed as per instructions provided by the manufacturer.

Results from the sample collected at the screening visit are used to determine eligibility. Samples collected at other time points, after Day 1, are used for efficacy analyses and to identify subjects who meet virologic failure criteria.

The nomenclature detailed in Table 7 will be used when describing HCV RNA levels:

Table 7 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 timepoints during the trial. Specific primary and secondary endpoints are:

- SVR_4 (Sustained Virologic Response 4 weeks after the end of all study therapy). The subject has HCV RNA < LLOQ 4 weeks after the end of all study therapy.
- SVR_8 (Sustained Virologic Response 8 weeks after the end of all study therapy). The subject has HCV RNA < LLOQ 8 weeks after the end of all study therapy.
- SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy). The subject has HCV RNA < LLOQ 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 24 weeks after the end of all study therapy.
- Virologic failure rate among subjects who do not discontinue study for non-treatment-related reasons at FW12.

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 having been achieved while 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 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 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

Resistance associated variants (RAVs) in the hepatitis C virus can lead to failure of therapy. This is one of the most important considerations when treating with a DAA. To better understand and document the potential for RAVs to impact treatment with MK-3682+MK-8408, blood samples for viral resistance assays are collected at Baseline (Day 1) to determine pre-existing RAVs to MK-3682 and MK-8408. Additional resistance testing on these samples may be performed. Blood samples for resistance testing are also collected during the follow-up period, as well as at the virologic failure confirmation visit (should this occur) for genotypic and investigational assays to assess emergence of resistance to MK-3682 and/or MK-8408 following treatment initiation. RAVs will be assessed for any subject who has detectable virus above 1000 IU/mL and has met a virologic failure criteria.

4.2.3.2 Safety Endpoints

The safety and tolerability of the study regimen will be assessed by a clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examinations, 12-lead electrocardiograms (ECGs), and standard laboratory safety tests at appropriate time points as specified in the Study 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 Pharmacokinetic Endpoints

The primary pharmacokinetic (PK) endpoint for MK-3682 (and metabolites) and MK-8408 is C_{trough}. PK samples will be collected from all subjects on each visit as described in the Study Flow Chart (Section 6.0) and in Table 12 (Pharmacokinetic Sampling Timepoints). These samples will be used to evaluate not only PK concentrations, but also PK/PD and PK/AE relationships of MK-3682 (and metabolites) and MK-8408, as appropriate. The pre-dose time points outlined were chosen in order to capture C_{trough} for all compounds. The frequency of C_{trough} collections will allow a thorough assessment of both subject drug concentrations and drug compliance, should a breakthrough occur. In addition, the post-dose time points, in conjunction with the other samples, will be used for PK-safety and PK-efficacy modeling.

4.2.3.4 Pharmacodynamic Endpoints

As described in Section 7.1.3.2.2, a subgroup of the study population will be included in an intensive viral kinetic sub-study. The purpose of this sub-study is to determine whether early viral kinetics can aid in developing a PK/PD model that can predict combinations which may be efficacious with various treatment durations.

These subjects will have HCV RNA samples collected during Week 1 as described in the Study Flow Chart (Section 6.0) and in Table 13 (Intensive Viral Kinetic Week 1 Sampling

Timepoints). In addition, PK samples will be collected as described in Table 12 (Pharmacokinetic Sampling Timepoints). These samples will be used to evaluate the PK/PD relationships of MK-3682 (and metabolites) and MK-8408, as appropriate.

4.2.3.5 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 IL28, genetic variants [46] will specifically be investigated for understanding variation in clinical endpoints for example, but not limited to, SVR and other efficacy safety and measurements.

4.2.3.6 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

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

There remains a critical need for new HCV therapies to address deficiencies in current therapy, including lower than optimal efficacy rates in select patient populations, drug resistance, and a lack of convenience. The two-drug, once-daily combination regimen containing MK-3682 (an HCV NS5B NI) and MK-8408 (an HCV NS5A complex inhibitor) has the potential to simplify treatment paradigms and reduce the need for pretreatment testing by providing a well-tolerated and efficacious regimen for multiple genotypes and diverse patient populations.

MK-3682

MK-3682 is a potent HCV NS5B NI with pangenotypic activity and a high barrier to resistance that, in combination with complementary HCV DAAs, has the potential to benefit an expanded spectrum of HCV-infected subjects, including those with currently difficult-to-treat GTs of HCV and individuals who have failed previous treatments. Among all the known DAA classes, NIs have displayed the broadest HCV genotypic coverage and the highest barrier to the development of resistance.

MK-3682 belongs to a class of uridine-based nucleotide analogs, e.g., SOF, that have been generally well tolerated. However, there have been postmarketing reports of symptomatic bradycardia, including one fatal cardiac arrest and cases requiring pacemaker insertion, in subjects taking the antiarrhythmic drug amiodarone together with either LDV/SOF or SOF in combination with another DAA. The toxicity potential of MK-3682 has been well characterized in *in vitro* mitochondrial toxicity assays, a battery of *in vitro* and *in vivo* genetic toxicity studies, safety pharmacology studies, and 4-week, 3-month and 6-month repeat-dose oral toxicity studies in rats and monkeys. In vitro and *in vivo* preclinical data demonstrate that MK-3682 and its metabolite, M6, at the exposures observed in the clinic, have limited potential for class toxicities associated with nucleotides, including myopathy and mitochondrial toxicity. NOAELs in the rat and Cynomolgus monkey at 1000 mg/kg/day provide adequate margins of safety relative to anticipated human doses and support daily oral dosing of humans for up to 6 months in duration. In summary, the toxicity studies identified minimal differences between control and treated animals, all of which were not considered adverse. Preclinical studies identified the liver and potentially kidney as potential target organs. There was no evidence of cardiovascular toxicity in studies up to 3 months duration, based on histopathology in the rat and monkey and echocardiography, electrocardiography, and serum biomarker evaluations in the monkey. Overall, the preclinical toxicity profile of MK-3682 via the oral route of administration supports the continuation of clinical trials.

To date, MK-3682 has been generally well tolerated in healthy subjects and HCV-infected subjects in several Phase 1 clinical studies at single doses up to 900 mg, multiple doses up to 750 mg per day for 10 days, and in Phase 2a trials of 300 mg or 450mg once daily for up to 24 weeks. Review of the safety data has revealed no clinically significant abnormalities in routine physical examinations including vital signs. There have been no dose-related or other patterns observed in the clinical, ECG or laboratory data. In the clinical studies proposed, available safety data (clinical and laboratory AEs, vital signs, laboratory safety tests, and ECGs) will be carefully monitored.

Phase 2 studies have demonstrated that a regimen of MK-3682 (450mg)/GZR/MK-8408 is highly effective in GT1, 2, and 3-infected subjects. Overall, MK-3682, as a component of a combination DAA regimen, has the potential to substantially improve HCV treatment outcomes, benefiting many HCV-infected individuals.

MK-8408

MK 8408 is a potent HCV NS5A complex inhibitor with pangenotypic activity that has the potential to benefit individuals requiring treatment of HCV infection, even if the individual is infected with currently difficult-to-treat GTs. The improved potency of MK-8408 against RAVs observed with earlier generation NS5A inhibitors suggests that MK-8408 will have

improved efficacy in individuals who have experienced treatment failures with other anti-HCV regimens and/or have NS5A RAVs at baseline.

MK-8408 has favorable safety findings in safety assessment toxicity studies and ancillary pharmacology studies, supporting the continued evaluation of MK-8408 in clinical trials in adults. The 2-week, 3-month, 6-month, and 9-month rat and dog toxicity studies provide substantial preclinical safety margins for doses proposed to be administered in future clinical trials. MK-8408 has been given to approximately 217 subjects and subjects in 8 MK-8408 Phase 1 trials and in over 800 subjects in ongoing Phase 2a trials (MK-8408 in combination with MK-3682 and GZR in HCV GT1, 2, and 3-infected subjects). MK-8408 has been administered at doses up to 600 mg/day (10 times the proposed clinical dose), 100 mg given daily for 10 days, and 60mg once daily for up to 24 weeks. No serious adverse experiences have been reported in any individual receiving MK-8408. There were no consistent treatment-related changes in labs, vital signs, or ECG safety parameter values. Adverse experiences in subjects receiving MK-8408 monotherapy have been mild to moderate in intensity and transient in duration. The totality of the safety data indicates that MK-8408 is well-tolerated.

Definitive embryo-fetal developmental toxicity studies conducted in concordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) M3 (R2) guidance have been completed in rats and rabbits for MK-3682 and MK-8408. Data support the inclusion of women of childbearing potential in clinical trials with MK-3682 and MK-8408. Inclusion of women of childbearing potential should be in accordance with the study protocol and applicable regulatory guidance.

Based on the preclinical data and the clinical experience to date in healthy subjects and HCV-infected subjects, the risk/benefit assessment is favorable for proceeding with the proposed clinical study with the two-drug combination of MK-3682+MK-8408.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (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 of at least 18 years of age with chronic HCV infection 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. have HCV RNA (≥ 10,000 IU/mL in peripheral blood) at the time of screening.
3. have documented chronic HCV GT1, GT2, GT3, GT4, GT5, or GT6 (with no evidence of non-typeable or mixed genotype) infection and meet the definition below:

- Positive for anti-HCV antibody, HCV RNA, or HCV GT1, GT2, GT3, GT4, GT5, or GT6 at least 6 months before Day 1

  OR

- Positive for anti-HCV antibody or HCV RNA with a liver biopsy consistent with chronic HCV infection (such as the presence of fibrosis) before Day 1

4. be otherwise healthy as determined by the medical history, physical examination, ECG, and clinical laboratory measurements performed at the time of screening.
5. have liver disease staging assessment as follows:

   Absence of cirrhosis is defined as any one of the following:

   - Liver biopsy performed within 24 months of Day 1 of this study showing absence of cirrhosis
   - Fibroscan performed within 12 months of Day 1 of this study with a result of ≤12.5 kPa
   - A Fibrosure® (Fibrotest®) score of ≤0.48 **and** aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) of ≤1 during Screening

   Compensated cirrhosis is defined as any one of the following:

   - A liver biopsy performed prior to Day 1 of this study showing cirrhosis (F4)
   - Fibroscan performed within 12 calendar months of Day 1 of this study with a result >12.5 kPa
   - A FibroSure® (Fibrotest®) performed during Screening with a score of >0.75 **and** an aspartate aminotransferase (AST): platelet ratio index (APRI) of >2. APRI formula: AST÷lab ULN for AST × 100÷ (platelet count÷100) (APRI calculation to be provided by the central laboratory)

     NOTE: In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy or Fibroscan is required. Liver biopsy results supersede the results obtained by Fibroscan® or Fibrosure®
6. be HCV treatment-naïve (defined as no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent) OR be HCV treatment-experienced (defined as prior virologic failure after treatment with an IFN-containing regimen, with or without ribavirin, or intolerance to an IFN-containing regimen). Subjects may not have previously received treatment with HCV direct-acting antiviral agents
7. meet one of the following criteria:

   a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

   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 or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner beginning at least 2 weeks prior to administration of the initial dose of study drug through 14 days after taking 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 their 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 two 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. understand the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.
9. provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

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

10. have HIV-1 infection documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry

(Day 1) 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 VL.

11. meet one of the following criteria:
    a. not currently be on antiretroviral therapy (ART) and have no plans 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 time of screening
    b. have well controlled HIV on ART, defined as:
        i. subjects on ART must have a CD4+ T-cell count >200 cells/mm^3 at time of screening
        ii. subjects on ART must have achieved and maintained virologic suppression (defined as confirmed HIV RNA level below the LLOQ of available assay at the time of screening) for at least 8 weeks prior to screening
        iii. subjects on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Day 1)
        iv. the combination ART regimen must not contain any antiretroviral medications other than: tenofovir, abacavir, lamivudine, emtricitabine, raltegravir, dolutegravir or rilpivirine

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. has evidence of decompensated liver disease manifested by the presence of or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver disease.
3. For cirrhotics: subjects that are Child-Pugh Class B or C, or who have a Pugh-Turcotte (CPT) score >6, must be excluded.

   NOTE: To calculate the Child-Pugh score, refer to the following website: http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality.
4. is coinfected with hepatitis B virus (e.g. HBsAg positive).
5. For subjects with HIV, has a history of opportunistic infection in the preceding 6 months prior to screening. A list of these events may be found in Appendix B of the following document: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

6. has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or carcinoma in situ; or is under evaluation for other active or suspected malignancy.
7. 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 prior to Day 1 is not available, imaging is required during screening.
8. is taking or plans to take any of the prohibited medications listed in Section 5.5 of the protocol or is taking herbal supplements, including but not limited to St. John's Wort (Hypericum perforatum), from 2 weeks prior to Day 1 through 2 weeks after the study treatment period.
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, in the opinion of the investigator, clinically-relevant drug or alcohol abuse within 12 months of screening.
11. is a female and is pregnant or breast-feeding, or expecting to conceive or donate eggs from at least 2 weeks prior to Day 1 through at least 14 days after the last dose of study drug, or longer if dictated by local regulations, OR is a male subject who is expecting to donate sperm or planning to impregnate female partner(s) from at least 2 weeks prior to Day 1 through 14 days after the last dose of study drug, or longer if dictated by local regulations.

    NOTE: After treatment allocation, female subjects should avoid conceiving or donating eggs and male subjects should avoid impregnating a partner or donating sperm for at least 14 days after taking the last dose of study drug.
12. has any of the following conditions:
    a. Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair.
    b. Poor venous access that precludes routine peripheral blood sampling required for this trial.
    c. Subject with a history of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).
    d. Any clinically significant cardiac abnormalities/dysfunction, including but not limited to: unstable angina, unstable congestive heart failure, and unstable arrhythmia.
    e. History of a medical/surgical condition that resulted in hospitalization within the 3 months prior to enrollment, other than for minor elective procedures.
    f. Medical/surgical conditions that may result in a need for hospitalization during the period of the study.

g. Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids, TNF antagonists, or other immunosuppressant drugs during the course of the trial.

h. Any condition, pre-study laboratory or ECG abnormality or history of any illness, which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drugs to the subject.

i. A life-threatening SAE during the screening period.

j. Evidence of history of chronic hepatitis not caused by HCV, including but not limited to drug-induced hepatitis, hemochromatosis, Wilson's disease, α1-antitrypsin deficiency, alcoholic liver disease and autoimmune hepatitis.

NOTE: Subjects with 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 8.

NOTE: If any of the laboratory exclusion criteria below in Table 8 are met, the site may have the abnormal value retested one time.

Table 8 Laboratory Exclusion Criteria

Laboratory Assessment	Exclusionary Values
Creatinine Clearance (estimated glomerular filtration rate, eGFR)[1]	<50 mL/min/1.73 m^2
Hemoglobin	<10 g/dL
Platelets	<50 × 10^3/μL
Total Bilirubin	>2.0 mg/dL unless history of Gilbert's disease (If Gilbert's disease is the proposed etiology, this must be documented in the subject's chart)
Serum Albumin	<3.0 g/dL
INR	>1.7 unless subject has a stable INR on an anticoagulant regimen
ALT	>10× ULN
AST	>10× ULN

[1] Creatinine clearance will be evaluated as an estimated GFR (eGFR) based on the modification of diet in renal disease (MDRD) equation:
eGFR (mL/min/1.73 m^2) = 175 × (Scr, std)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if black)
Scr, std: serum creatinine measured with a standardized assay

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 treatment to be used in this trial is outlined in Table 9.

Table 9 Trial Treatment for Each Arm

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3682	450mg (3 x 150mg tablet)	QD	Oral	12 weeks	Experimental
MK-8408	60mg (6 x 10mg capsule)	QD	Oral	12 weeks	Experimental

The first dose of trial treatment will be administered at the trial site at Visit 2 (Day 1). The doses to be taken at other visits at which a pre-dose PK sample is to be collected will also be administered at the trial site. All other dosing will be performed by the subject (i.e., unsupervised at his/her home) in the morning at approximately the same time each day for MK-3682 and MK-8408.

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 to each subject.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Dose modification of MK-3682 or MK-8408 is not permitted. See Section 5.2.2 for instructions if for any reason MK-3682 or MK-8408 needs to be interrupted. For any other dose modifications that occur, consult the Sponsor Protocol team.

5.2.2 Timing of Dose Administration

All doses of MK-3682 and MK-8408 should be taken on an empty stomach after an overnight fast, at least 1 hour before the morning meal. Study medications should be taken with water but without food. In addition, subjects should fast overnight prior to reporting to the study site for dosing on Treatment Day 1 (Visit 2) and for all other visits at which a pre-dose PK sample is to be collected. For study visits after Visit 2, if there are cases in which a morning visit is not feasible and a subject is seen in the afternoon, the subject should take their study medication in the morning, after an overnight fast, as per their regular schedule; PK samples will still be collected during these visits.

If a subject misses a dose of MK-3682 or MK-8408 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 a subject misses a dose of MK-3682 or MK-8408 and it is greater than 8 hours before the next dose, the missed dose should be taken at least 2 hours after last meal and 1 hour before next meal and the normal dosing schedule resumed.

If for any reason MK-3682 or MK-8408 needs to be interrupted, the entire regimen should be interrupted and can be interrupted for up to 3 days. If the interruption lasts for more than 3 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

All subjects will receive a treatment regimen of MK-3682 (450mg) + MK-8408 (60mg) co-administered concomitantly as separate medications once-daily for 12 weeks. Subjects will be assigned to treatment arms based on genotype.

Documentation of treatment period entry will occur centrally using a computer generated allocation schedule to assign a treatment/allocation number.

5.4 Stratification

Although there is no randomization, subjects are classified (stratified) by genotype to determine assignment to treatment arm by design. No other stratification based on age, sex, or other characteristics will be used in this trial.

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 or have taken since the last visit.
- 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.nih.gov website.

Specific restrictions for concomitant therapy during the course of the trial are listed. These are based on the current known metabolism of the drugs as described.

Restrictions may be removed if indicated by emergent data from drug-drug interaction trials. Any medications/therapies no longer contraindicated will be communicated to the site by an administrative letter.

The following medications/therapies are not permitted from 2 weeks prior to Day 1 through 2 weeks after the study treatment period.

Known hepatotoxic drugs, including but not limited to:

- etifoxine
- isoniazid
- nitrofurantoin

Herbal supplements

Antiarrhythmic agents (including but not limited to amiodarone, quinidine, bepridil, disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone)

Strong inhibitors of CYP3A, including but not limited to:

- clarithromycin
- telithromycin
- itraconazole
- ketoconazole
- nefazodone

Strong and moderate CYP3A inducers, including but not limited to:

- anti-infectives: nafcillin, rifampin
- anticonvulsants: carbamazepine, phenytoin, phenobarbital
- bosentan
- modafinil
- St. John's Wort

Gastric acid modifiers

- H2 blockers
- proton-pump inhibitors

  Note: antacids, such as calcium carbonate or aluminum hydroxide-based product, will be allowed during the study, but it is recommended they be taken either 4 hours before or after dosing of MK-3682 and MK-8408 (see Allowed Medication below)

HIV medications (note that not all prohibited HIV medications are listed):

- efavirenz
- etravirine
- nevirapine
- ritonavir
- all boosted and unboosted HIV protease inhibitors

  Note: the only permitted HIV medications are tenofovir, abacavir, lamivudine, emtricitabine, raltegravir, dolutegravir and rilpivirine

HMG-CoA reductase inhibitors (statins):

- rosuvastatin greater than 10 mg (see Allowed Medications below)
- atorvastatin, simvastatin, lovastatin, or fluvastatin greater than 20 mg (see Allowed Medications below)

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.

Allowed Medications:

The following concomitant medications are allowed in this study:

Antihypertensives:

- ACE inhibitors/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: amlodipine, diltiazem, verapamil

  Note: for other calcium-channel blockers, please consult with the Sponsor
- hydralazine, clonidine, minoxidil, isosorbide nitrates

Anemia: erythropoetin

Diuretics: hydrocholorothiazide, 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:

- antacids (stomach acid neutralizers, such as calcium carbonate or aluminum hydroxide-based products) are permitted, but it is recommended that they be taken either 4 hours before or after dosing of MK-3682 and MK-8408

HMG-CoA reductase inhibitors (statins):

- pravastatin and pitavastatin: may be coadministered without dose adjustment
- rosuvastatin: use the lowest possible effective dose of rosuvastatin, but do not exceed a daily dose of 10 mg
- atorvastatin, simvastatin, fluvastatin, lovastatin: use the lowest possible effective dose of atorvastatin, but do not exceed a daily dose of 20 mg

Anti-coagulants: warfarin, heparin, low molecular weight heparin, aspirin, fondaparinux, desirudin, acenocoumarol

Opiate substitution therapy: Subjects on stable doses of methadone or buprenorphine/naloxone may be enrolled in this study, if not excluded under Exclusion Criterion 10 in Section 5.1.3.

Given that this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or 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

MK-3682 and MK-8408 should be taken on an empty stomach after an overnight fast and at least 1 hour before the morning meal. Study medication should be taken with water but without food.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial if:

- The subject or legal representative (such as parent or legal representative) withdraws consent.

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

Table 10 provides reasons why a subject must be discontinued from treatment but should continue to be monitored in the trial, as well as reasons why a subject must be discontinued from treatment and the trial.

Table 10 Discontinuation Scenarios

Reason for Discontinuation Scenario	Action
The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.	Discontinue from Treatment and Trial
Subject meets criteria for HCV virologic breakthrough or rebound (see Section 4.2.3.1.1.2)	Discontinue from Treatment (should continue to monitor in the trial)
Subject becomes pregnant during the trial.	Discontinue from Treatment (should continue to monitor in the trial)
A physician investigator feels it is in the best interest of the subject to discontinue.	Discontinue from Treatment (should continue to monitor in the trial)
The subject's ALT or AST increases to >500 IU/L and is confirmed with repeat test within one week.	Discontinue from Treatment (should continue to monitor in the trial)
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).	Discontinue from Treatment (should continue to monitor in the trial)
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.	Discontinue from Treatment (should continue to monitor in the trial)
The subject's serum creatinine increases to Grade 3 or higher (>1.8× upper limit of normal), confirmed with repeat test within one week.	Discontinue from Treatment (should continue to monitor in the trial)
The subject's creatinine clearance (eGFR) decreases to <30 mL/min/1.73 m^2, confirmed with repeat test within 1 week. Creatinine clearance will be evaluated as an estimated GFR (eGFR), based on the modification of diet in renal disease (MDRD) equation: eGFR (mL/min/1.73 m^2) = 175 × (Scr, std)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if black) Scr, std: serum creatinine measured with a standardized assay	Discontinue from Treatment (should continue to monitor in the trial)
The subject has a Grade 4 laboratory AE, or a life-threatening clinical AE, or an AE that results in or prolongs an existing in-subject hospitalization, that is assessed to be a study drug-related laboratory or clinical AE.	Discontinue from Treatment (should continue to monitor in the trial)
SAE assessed by the physician investigator as possibly or probably related to study medication. Investigator may continue the subject in the trial, if it is deemed to be in the best interest of the subject to stay on the study treatment after consultation with Sponsor.	**May** Discontinue from Treatment (should continue to monitor in the trial)
Failure to comply with the dosing, evaluations, or other requirements of the trial.	**May** Discontinue from Treatment (should continue to monitor in the trial)

NOTE: 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 study unless there is a requirement for prohibited concomitant medications (see Section 5.5) to construct a new HIV treatment regimen.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

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

Early trial termination will be the result of the criteria specified as follows.

5.11.1 Safety Criteria for Pausing Enrollment

If ≥3 subjects receiving MK-3682 and MK-8408 experience any of the following, assignment of new subjects into that arm will be paused. Subjects that are tolerating treatment may continue to receive study therapy, but no additional subjects will be enrolled into that arm until the Sponsor has reviewed all safety data on subjects, including:

- Life threatening clinical AEs, or an event that results in or prolongs an existing in-subject hospitalization, or deaths that are assessed to be study drug-related
- Grade 4 laboratory AEs that are assessed to be study drug-related laboratory AEs

5.11.2 Safety Criteria for Stopping Enrollment and Early Trial Termination

If a total of ≥12 subjects (~5%) in the 12-week arms of MK-3682+MK-8408 experiences any of the following, the trial will terminate.

- ALT or AST increases to >500 IU/L and is assessed to be study drug related
- The subject's serum creatinine increases to Grade 3 or higher (>1.8× upper limit of normal), confirmed with repeat test within 1 week
- The subject has a Grade 4 laboratory AE, or a life-threatening clinical AE, or an AE that results in or prolongs an existing in subject hospitalization, or death, that is assessed to be study drug-related
- The subject's creatinine clearance decreases to <30 mL/min/1.73 m^2, confirmed with repeat test within 1 week. Creatinine clearance will be evaluated as an estimated GFR (eGFR), based on the modification of diet in renal disease (MDRD) equation:

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

  Scr, std: serum creatinine measured with a standardized assay

5.11.3 Efficacy Criteria for Stopping Enrollment

- If a total of ≥2 out of the first 10 HIV-infected subjects in the PP population across all arms experience confirmed loss of HIV-1 virologic suppression, then no additional HIV/HCV co-infected subjects will be enrolled. Loss of virologic suppression is defined as HIV-1 RNA ≥200 copies/mL, confirmed on 2 consecutive tests at least 2 weeks apart in subjects compliant with their HIV ARV therapies. Remaining co-infected subjects who are already on trial treatment would continue HCV treatment regimen while their HIV regimen is being reassessed.
- If a total of ≥3 out of the first 10 subjects in the PP population enrolled in a 12-week dosing duration arm experience virologic non-response, rebound, breakthrough or relapse by FW4, no further subjects will be enrolled in that 12-week treatment arm.

5.12 Clinical Criteria for Trial Modification

5.12.1 Efficacy Criteria for Modification of Treatment Duration

- If a total of ≥3 out of the first 10 subjects in the PP population enrolled in a 12-week dosing duration arm experience virologic relapse by FW4, the treatment duration of any remaining subjects of that genotype in that arm will be extended to 16 weeks and no further subjects will be enrolled in that 12 week treatment arm.

6.0 TRIAL FLOW CHART

		1st Week					Treatment Weeks								Follow-Up Weeks						Unscheduled	
Main Study Population 12-week Treatment			NA	NA	NA																	
Intensive Viral Kinetic subgroup	Screening	Day 1[8]	Day 2[12]	Day 3[12]	Day5[12]	Day 7	2	4	6	8	10	12	14[13]	16[13]	FW4	FW8	FW 12	FW 16[14]	FW 20[14]	FW 24	HCV/HIV Viral Failure Confirmation Visit[9,10]	Early Discontinuation Visit[9, 11]
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Visit Windows	NA	NA	NA	+2d	-1 to +2d	-2 to +2d	-4 to +7d	-7 to +7d	-7 to +7d	-7 to +14d	-7 to +14d	-7 to +14d	-7 to +14d	-7 to +14d	-1 to +2 weeks						NA	NA
ADMINISTRATIVE PROCEDURES																						
Informed Consent	x																					
Informed Consent for Future Biomedical Research (FBR)	x																					
Inclusion/Exclusion Criteria	x																					
Subject Identification Card	x																					
Medical History	x																					
Prior and Con-med Review	x	x				x	x	x	x	x	x	x	x	x	x						x	x
Treatment Allocation		x																				
Review Study Medication Diary		x				x	x	x	x	x	x	x	x	x								x
Distribute Study Medication Diary		x					x	x	x	x	x	x[15]	x									
CLINICAL SAFETY EVALUATIONS																						
Physical Examination[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]			x[1]	x[1]	x[1]
Weight	x	x																				x
Height	x																					

		1st Week					Treatment Weeks								Follow-Up Weeks						Unscheduled	
Main Study Population 12-week Treatment			NA	NA	NA																	
Intensive Viral Kinetic subgroup	Screening	Day 1[8]	Day 2[12]	Day 3[12]	Day5[12]	Day 7	2	4	6	8	10	12	14[13]	16[13]	FW4	FW8	FW 12	FW 16[14]	FW 20[14]	FW 24	HCV/HIV Viral Failure Confirmation Visit[9,10]	Early Discontinuation Visit[9, 11]
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Visit Windows	NA	NA	NA	+2d	-1 to +2d	-2 to +2d	-4 to +7d	-7 to +7d	-7 to +7d	-7 to +14d	-7 to +14d	-7 to +14d	-7 to +14d	-7 to +14d	-1 to +2 weeks						NA	NA
12-Lead ECG	x						x	x		x		x		x	x							x
Vital Signs	x	x				x	x	x	x	x	x	x	x	x	x	x	x			x		x
Subject confirmation of birth control	x	x				x	x	x	x	x	x	x	x	x	x						x	x
Review SAEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Telephone contact																		x	x			
LABORATORY SAFETY EVALUATIONS																						
Coagulation (PT & INR)	x	x				x	x	x	x	x	x	x	x	x	x		x			x	x	x
Chemistry & Hematology	x	x				x	x	x	x	x	x	x	x	x	x	x	x			x	x	x
HBsAg	x																					
HIV-1 Serology	x																					
Urinalysis		x				x	x	x	x	x	x	x	x	x	x		x				x	x
Urine Pregnancy Test (females of child bearing potential only)	x	x						x	x	x	x	x	x	x	x						x	x
PHARMACOKINETICS																						
MK 8408 PK		x		x[12]		x	x	x	x	x	x	x	x	x							x[9]	x[9]
MK-3682 and metabolites PK		x		x[12]		x	x	x	x	x	x	x	x	x							x[9]	x[9]
Meal Information for PK		x		x[12]		x	x	x	x	x	x	x	x	x							x[9]	x[9]

		1st Week					Treatment Weeks								Follow-Up Weeks						Unscheduled	
Main Study Population 12-week Treatment			NA	NA	NA																	
Intensive Viral Kinetic subgroup	Screening	Day 1[8]	Day 2[12]	Day 3[12]	Day5[12]	Day 7	2	4	6	8	10	12	14[13]	16[13]	FW4	FW8	FW 12	FW 16[14]	FW 20[14]	FW 24	HCV/HIV Viral Failure Confirmation Visit[9,10]	Early Discontinuation Visit[9, 11]
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Visit Windows	NA	NA	NA	+2d	-1 to +2d	-2 to +2d	-4 to +7d	-7 to +7d	-7 to +7d	-7 to +14d	-7 to +14d	-7 to +14d	-7 to +14d	-7 to +14d	-1 to +2 weeks						NA	NA
HCV EVALUATIONS																						
HCV Genotype Determination	x																					
Liver imaging[2]	x																					
HCV RNA Level[3]	x	x	x[12]	x[12]	x[12]	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x[11]
Plasma for HCV Viral Resistance and Biomarkers[4]		x													x	x	x			x	x	x[11]
Blood for genetic analysis[4]		x																				
HIV EVALUATION[5]																						
HIV RNA	x	x					x	x	x	x	x	x	x	x	x	x	x			x	x	x
Plasma for HIV Viral Resistance																					x[10]	
CD4+ T-Cell Counts	x	x						x		x		x	x	x	x		x			x		x
DRUG ADMINISTRATION[16]																						
MK-3682 (open-label)		x[6]	x	x	x	x	x[6]	x[6]	x[6]	x[6]	x[6]	x[6,7]	x[6]	x[7]								
MK-8408 (open-label)		x[6]	x	x	x	x	x[6]	x[6]	x[6]	x[6]	x[6]	x[6,7]	x[6]	x[7]								

[1] A comprehensive PE will be done at screening. For all other visits a focused PE will be conducted when clinically indicated.
[2] For cirrhotic subjects imaging must be performed within 6 months prior to treatment allocation to rule out hepatocellular carcinoma.
[3] Blood samples will be collected for HCV viral resistance testing at baseline, viral failure confirmation visits, and follow-up visits. 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 FBR if the subject signs the FBR consent.

[4] Blood sample will be collected for IL28 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 variation and drug response. Leftover extracted DNA will be stored at the end of the study for FBR if the subject consents to FBR.
[5] Blood samples will be collected for HIV RNA and CD4+ T-cell counts as part of the screening visit for all subjects. HIV evaluations will only be performed at subsequent visits in subjects that are HIV co-infected.
[6] Study drug is to be dispensed at Day 1, Week 2, Week 4, Week 6, Week 8 and Week 10 visits for all subjects receiving 12 weeks of treatment. If it is determined that the treatment duration will be 16 weeks, study drug will also be dispensed at Week 12 and Week 14 visits.
[7] After the last dosing visit, subjects proceed to the follow up visit schedule.
[8] Procedures at visit 2, Day 1 should be performed prior to the first dose unless specified otherwise.
[9] Pharmacokinetic samples and meal information for PK are to be collected at HCV/HIV viral confirmation or early discontinuation visits that occur only during the study treatment period.
[10] In subjects that are HIV co-infected, blood samples will be collected for HIV viral resistance at the time of HIV RNA failure confirmation visit.
[11] If a subject is confirmed viral failure during therapy (i.e., break through), then sample collection for HCV RNA and Viral Resistance/Biomarker is not needed for the early discontinuation visit.
[12] Visits on Day 2, Day 3 and Day 5 are applicable to intensive viral kinetic subgroup only.
[13] Treatment week 14 and 16 are only applicable if it is determined during the study that the treatment duration needs to be extended to 16 weeks.
[14] FW16 and FW20 visits are virtual visits. The study nurse will have telephone contact with the subject to make sure that he/she is doing well and provide a reminder for the FW24 visit.
[15] If it is determined that the treatment duration needs to be extended to 16 weeks, Study Medication Diaries will be distributed at the treatment week 12 visit for subjects that will receive 16 weeks of treatment.
[16] MK-3682 and MK-8408 open-label bottles provided by the SPONSOR cover a maximum of 18 days of dosing (2w + 4 days). 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 drugs as defined by the length of the assigned treatment regimen.

Long Term Follow-Up Subjects with Virologic Failure	Follow-up Period Month M12	M18	M24	M30	M36	Unscheduled Visit
Visit Number	**23**	**24**	**25**	**26**	**27**	**28**
Visit Window	-3 to +3 months					**NA**
ADMINISTRATIVE PROCEDURES						
Long-Term Follow-Up Informed Consent[1]	**x**					
Review HCV Medications/Therapies	**x**	**x**	**x**	**x**	**x**	**x**
CLINICAL EVALUATIONS						
Focused Physical Examination (PE)[2]	**x**		**x**		**x**	
Vital Signs (heart rate, blood pressure, temperature)	**x**		**x**		**x**	
Review Serious Adverse Events[3]	**x**	**x**	**x**	**x**	**x**	**x**
LABORATORY SAFETY EVALUATIONS						
Coagulation (PT & INR)	**x**		**x**		**x**	
Chemistry & Hematology	**x**		**x**		**x**	
HCV EVALUATIONS						
HCV RNA[4]	**x**	**x**	**x**	**x**	**x**	
Plasma for HCV Viral Resistance[4]	**x**	**x**	**x**	**x**	**x**	

HCV = hepatitis C virus, INR = international normalized ratio, M = long-term follow-up month, PT = prothrombin time, SAE =Serious adverse event

1 Subjects who take at least 1 dose of study drug, experience virologic failure, complete FW24, AND agree to participate in the long-term follow-up period of the study must sign a separate Informed Consent. This must occur prior to performing any procedures in the long-term follow-up period.

2 A focused PE will be conducted when clinically indicated at the subject's annual visits.

3 Serious Adverse Events will be collected per requirements in Section 7.2; the reporting timeframe for serious adverse events is described in Section 7.2.3.1.

4 Blood samples will be collected for HCV viral resistance testing if the subject has quantifiable HCV RNA.

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 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.

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 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 allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation. 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 to be completed during the study period. The investigator/study coordinator will be responsible for entering the subject's identification (allocation number), visit number, and the dates before giving the diary to the subject. The subject will be instructed to record dates/times and the number of tablets or capsules of study drug doses in the diary for the entire time period. Only the subject should enter information into the diary. The subject is to return the completed diary at each scheduled visit. At visits when used/unused study medications are returned, site personnel must verify the accuracy of the dosing diary by comparing entries with amounts of returned study medication. If a discrepancy is noted, 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 diary. The investigator/study coordinator will be responsible for transferring the appropriate information from the diary card onto the appropriate case report form.

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 will be witnessed by the investigator and/or trial staff at the Day 1 visit and on all PK visits during which a pre-dose sample will be collected.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

All physical examinations 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 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 exams should be performed when clinically indicated. For all other visits, a focused exam will be performed when clinically indicated. Any significant changes between the screening visit and Day 1 should be noted in the Medical History electronic case report form (eCRF). Any significant changes after receiving study therapy at Day 1 must be reported as adverse events and entered on the adverse event eCRF. If the subject is

discontinued for any reason during the treatment phase, 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 flow chart. Clinically significant changes from Day 1 should also be captured as adverse events in the eCRF.

7.1.2.3 12-Lead ECG

Special care must be taken for proper lead placement. Subjects should be shaved as necessary for proper lead placement. Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained. However, clinically significant findings from the screening ECG must be captured in the medical history eCRF. For ECGs performed during treatment or during the follow-up period, any clinically significant changes compared with the screening ECG must be captured as adverse events.

7.1.2.4 Vital Signs

Vital signs will include heart rate, blood pressure, and oral temperature.

Note: Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, and axillary temperatures 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 adverse event.

7.1.2.5 Birth Control Confirmation

Confirmation must be obtained by site personnel that subjects and their partner(s) 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.

7.1.2.6 Adverse Events

For details on assessing and recording adverse events please refer to Section 7.2.

7.1.2.7 Non-Invasive 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. [47] in a population of subjects with chronic hepatitis C, a cut-off of 12.5 kPa was selected for cirrhotics. At this cut-off, the sensitivity and specificity of the test for cirrhosis were 87% and 91%, respectively, and the negative predictive value was 95%. Since this analysis was assessed specifically in subjects with chronic hepatitis C, the cut-off value ≤12.5 kPa used by Castera was selected to exclude 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 subjects 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 [48]. 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 subjects would need a liver biopsy to confirm the diagnosis of cirrhosis. The cut-off values for excluding cirrhotics using the two 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 cut-off values will differentiate cirrhotic from non-cirrhotic subjects 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 below. 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 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 11.

Table 11 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Bilirubin	Hepatitis C Virus Genotype
Hemoglobin	Alkaline phosphatase	Blood	HBsAg (screening only)
Platelet count	Alanine aminotransferase (ALT)	Glucose	HIV-1 serology (screening only)
WBC (total and differential)	Aspartate aminotransferase (AST)	Ketone	Prothrombin time
Erythrocytes (RBC count)	Creatinine	Leukocyte Esterase	International Normalized Ratio (INR)
	Creatinine Clearance (estimated glomerular filtration rate, GFR)	Nitrites	Choriogonadotropin Beta (Urine pregnancy test kits to sites)
	Creatine Kinase	pH	Serum human chorionic gonadotropin (reflex when urine pregnancy test is "positive")
	Gamma-glutamyltransferase	Protein	Plasma HCV RNA
	Glucose (serum glucose)	Specific Gravity	Fibrosure® (Fibrotest) as requested by site for entry criteria (may be performed locally)
	Amylase	Bacteria	APRI calculation (screening only)
	Lipase	Squamous Epithelial Cells	CD4+ T-cell count (at screening in all subjects, then in co-infected subjects only at subsequent visits)
	Potassium	RBC	Plasma HIV-1 RNA (at screening in all subjects, then at subsequent visits in coinfected subjects only)
	Sodium	WBC	
	Total Bilirubin		
	Direct Bilirubin		
	Indirect Bilirubin		
	Total protein		
	Blood Urea Nitrogen		

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics will be collaboratively determined by the Departments of Quantitative Pharmacology and Pharmacometrics and the appropriate department within Clinical

Research. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional PD markers.

7.1.3.2.1 Blood Collection for Plasma MK-3682 (and metabolites) and MK-8408

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

Pharmacokinetic samples will be collected from all enrolled subjects according to the PK sampling schemes shown in Table 12. Subjects participating in an intensive viral kinetic sub-study will be providing additional PK samples on Days 3 and 7 that are not being collected from the other subjects in the study. The intensive viral kinetic substudy will include the first 10 GT1, 10 GT2, 10 GT3 and up to the first 5 GT4, 5 GT5 and 5 GT6 subjects who consent to participate.

On all PK visits where a pre-dose sample will be collected, the subject must withhold their dose on the day of the PK visit; the dose will be administered at the site after collection of the pre-dose PK sample. For study visits after Visit 2, if there are cases in which a morning visit is not feasible and a subject is seen in the afternoon, the subject should take their study medication in the morning, after an overnight fast, as per their regular schedule (in accordance with Section 5.2.2 Timing of Dose Administration) and PK samples will still be collected during these afternoon visits.

All PK samples will be used to evaluate not only PK exposures but also to assess the PK/PD and PK/AE relationships of MK-3682 (and metabolites) and MK-8408. The date and time of each PK sample as well as the date and time of the last dose of MK-3682 and MK-8408 prior to the PK sample will be recorded.

When predose PK samples are collected, information regarding meal qualitative fat content and time of the meal consumed within 5 hr before and 2 hr after the subject's last dose of MK-3682 and MK-8408 prior to the PK samples will be recorded; when postdose PK samples are collected, information regarding meal qualitative fat content and time of the meal consumed within 5 hr before and 2 hr after the subject's last dose of MK-3682 and MK-8408, as appropriate, which is administered at the study site will be recorded also. For subjects who may take multiple meals during the time window, only the meal closest to the last dose prior to the PK samples will be recorded.

Table 12 Pharmacokinetic Sampling Timepoints

Visit Number	Study Day/Week	Time Relative to Dose of MK-3682/MK-8408[3, 4]	PK Timepoints for Non-Intensive Viral Kinetic Subjects	PK Timepoints for Intensive Viral Kinetic Subjects
2	Day 1	Pre-dose	x	x
4	Day 3	Pre-dose		x
6	Day 7	Pre-dose	x	x
		0.5-, 2-, and 4-hour[5] post-dose		x
7	Week 2	Pre-dose	x	x
8	Week 4	Pre-dose	x	x
		0.5- and 2-hour post-dose[5]	x	x
9	Week 6	Pre-dose	x	x
10	Week 8	Pre-dose	x	x
11	Week 10	Pre-dose	x	x
12	Week 12	Pre-dose	x	x
13[1]	Week 14	Pre-dose	x	x
14[1]	Week 16	Pre-dose	x	x
21	HCV/HIV Viral Failure Confirmation Visit[3]	NA	x[2]	x[2]
22	Early Discontinuation Visit[3]	NA	x[3]	x[3]

[1] If the treatment duration is increased to 16 weeks, Visit 13 (Week 14) and Visit 14 (Week 16) PK samples will be collected.
[2] PK samples and meal information for PK are to be collected at HCV/HIV viral confirmation or early discontinuation visits that occur only during the study treatment period.
[3] Time relative to last dose of MK-3682 and MK-8408 must be recorded in the electronic case report form.
[4] After study Visit 2, if there are cases in which a morning visit is not feasible and a subject is seen in the afternoon, the subject should take their study medication in the morning, after an overnight fast, as per their regular schedule (in accordance with section 5.2.2 Timing of Dose Administration) and PK samples will still be collected during these afternoon visits.
[5] 0.5 hour samples may be taken ± 5 minutes, 2 hour and 4 hour post-dose samples may be taken ± 15 minutes.
Note: ~4 mL of blood will be collected at each specified time point for plasma PK assessment of MK-3682 (and metabolites).
~4 mL of blood will be collected at each specified time point for plasma PK assessment of MK-8742 or MK-8408.
Note: The date and time of the PK sample collection for all MK-3682 (and metabolites) and MK-8408 PK samples must be recorded in the electronic case report form.
Note: At the time of PK sample collection, subjects will be asked to provide information regarding the time/date of the last MK-3682 and MK-8408 dose prior to the PK sample collection. (This can also be obtained by referencing the subject's study medication diary).

7.1.3.2.2 Intensive Viral Kinetic Sub-Study

A subgroup of the study population will be included in an intensive viral kinetic sub-study. Approximately ten subjects who are GT1-infected (two of whom are cirrhotics), ten GT2, ten GT3 (two of whom are cirrhotics) and up to five subjects each who are GT4, GT5 or GT6-infected, will be asked to participate in order of allocation until we have reached the targeted numbers per genotype. The data from this sub-study will be used to validate the existing viral dynamics model for MK-3682 and MK-8408.

These subjects will have HCV RNA samples collected during Week 1 as shown in Table 13:

Table 13 Intensive Viral Kinetic Week 1 Sampling Timepoints

Visit Number	Study Day	Time Relative to Dose of MK-3682/MK-8408
2 and 3	Starting on Day 1 and completing on Day 2	Pre-dose and 2, 4, 8, 12, 24, and 32 hours post-dose*
4	Day 3	Pre-dose
5	Day 5	Pre-dose
6	Day 7	Pre-dose
*Post-dose samples may be taken ±15 minutes for each time point.		

HCV RNA samples also will be collected at the Week 2, 4, 6, 8, 10 and 12 visits. If the treatment duration is extended to 16 weeks, HCV RNA samples will be collected at the Weeks 14 and 16 visits during treatment.

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

7.1.3.3 HCV Evaluation

The following specimens are to be obtained 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 Abbott HCV Real Time Genotype II assay which 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 RT-PCR assay. The RT-PCR reaction uses 3 sets of HCV specific amplification primers targeting the conserved 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 4, 89% for GT5 and 83% for GT6 with 100% specificity in HCV serologically negative plasma samples. Phylogenetic analyses will be performed using sequences for NS3, NS5A and NS5B to ensure accurate assignment of sample genotype/subtype.
- Blood must be drawn from each subject to assess HCV RNA plasma levels at various time points as shown in the study flow chart. HCV RNA in plasma will be measured using a COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0 ® 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 future biomedical research only if the subject signed for future biomedical 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 future biomedical research only if the subject signed for future biomedical 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 DNA may be used for future biomedical research only if the subject signed for future biomedical research consent.

Note: Samples may also be used for future assay development and validation if the subject signed for future biomedical research consent.

7.1.3.4 HIV Evaluation

The following specimens are to be obtained:

- Blood must be drawn from each subject to assess HIV RNA plasma levels at various time points as shown in the study flow chart (Section 6). HIV RNA in plasma will be measured using a COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2. 0 assay with a lower limit of quantification of 20 IU/mL.
- Blood must be drawn from each subject at HIV RNA viral failure confirmation visit (in case of potential failure, defined as HIV-1 RNA ≥ 200 copies/mL, confirmed on 2 consecutive tests at least 2 weeks apart in subjects compliant with their HIV ART) to assess viral resistance mutations, and processed as instructed by the central laboratory manual. HIV-1 drug resistance will be assessed using the PhenoSense GT™ HIV Assay, and the Genosure Prime Assay.
- Blood must be drawn from each subject to assess immunologic status. CD4+ T-cell counts will be obtained at screening and at various time points as shown in the flow chart.

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 copies/mL

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 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

- 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 as detailed in Section 7.1.5.4.

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 PPD, 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 Subject Blinding/Unblinding

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

7.1.4.3 Domiciling

The subjects who are participating in the Intensive Viral Kinetic sub-study will report to the clinical research unit (CRU) on the morning of Day 1 prior to trial drug administration and will remain either in the unit or in a local facility until completion of the 32-hour blood draw after the first dose of study medication. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

None.

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 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. 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 for 14 days after the last dose of study medication, or longer if dictated by local regulations.

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 Study Flow Chart must be completed and subject eligibility confirmed by the investigator prior to the subject's 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
- HbsAg
- HIV-1 serology
- Liver biopsy/Fibroscan/ FibroSure® (Fibrotest®)
- Liver imaging
- 12-Lead ECG

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

Treatment Day 1 (Visit 2)

Subjects should fast overnight prior to reporting to the study site for dosing on Treatment Day 1 (Visit 2).

Pre- and Post-Treatment Procedures

Day 1 procedures listed on the Study 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 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 or allocated to treatment in the study.

Blood and urine will be collected for assay of safety evaluations, plasma HCV RNA, plasma HIV RNA, and PK measurements. These samples will be sent to the appropriate central laboratory(ies) 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 MK-3682 and MK-8408.

7.1.5.4 Discontinued Subjects Continuing to be Monitored in the Trial

Discontinuation during Treatment Period

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, the following information should be collected:

- 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.

Discontinuation for Virologic Failure

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, 8, 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, 8, 12, and 24 weeks) as outlined in the Trial Flow Chart (Section 6.0).

All subjects who take at least 1 dose of study drug, experience virologic failure, and complete FW24 should be offered long-term follow-up (see Section 7.1.5.6).

Discontinuation during Follow-Up Period(s)

Subjects who discontinue during the follow-up period (e.g. follow-up visits at 4 through 24 weeks after EOT) for reasons other than virologic failure should complete an Early Discontinuation Visit as outlined in the Trial Flow Chart. Subjects who discontinue from the long-term follow-up period (e.g. through 3 years after EOT) should complete an Unscheduled Visit as outlined in the Long-Term Follow up section of the Trial Flow Chart.

At a minimum, the following information should be collected:

- The reason the subject discontinued
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate
- SAEs (per reporting requirements outlined in Section 7.2)

Discontinuation of Long Term Follow-Up

Amendment 04 implemented the discontinuation of the LTFU period. Subjects who already entered the LTFU section of the trial are to be discontinued (via an unscheduled visit). No further subjects will be entered into the LTFU period.

7.1.5.5 Post-Trial

At the completion of study therapy subjects will return to the study site for follow-up visits at 4, 8, 12, and 24 weeks after the last dose of study drug. Virtual visits by telephone will occur at follow-up weeks 16 and 20.

7.1.5.6 Long-Term Follow-Up

To assess the persistence of RAVs over time, follow-up in this study will be extended to a total of -3 years and offered to any subject who meets all of the following:

- Has taken at least 1 dose of study drug (MK-3682 or MK-8408)
- Experienced virologic failure
- Completed the FW24 visit

Subjects must read and sign a separate informed consent before being allowed to participate in the long-term follow-up. There are a total of 5 additional study visits at Long-term Follow-up Month 12, 18, 24, 30, and 36 after end-of-treatment. Subjects who complete treatment, experience virologic failure, and complete long-term follow-up of this trial can expect to participate for a total of approximately 175 weeks.

As of amendment 04, the long term follow up period is being discontinued. Any subject who has consented to participate in the Long Term Follow Up will be discontinued via an unscheduled visit.

Monitoring during these long-term follow-up visits will include assaying HCV RNA and resistance testing. For safety assessments, SAEs will be collected in accordance with the safety requirements outlined in Section 7.2, along with a yearly directed physical examination and laboratory testing. Subjects participating in the long-term follow-up will be discontinued from the study if they receive HCV treatment at any time during the long-term follow-up.

7.1.5.7 Evaluation of Laboratory Safety Signals

Laboratory safety measurements will be made after the first week of treatment, followed by every 2 weeks for the entire treatment period, and during the follow-up period to assess potential liver and renal safety signals as outlined in the flow chart.

If a subject has one or more of the laboratory events of clinical interest (ECI) (refer to 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 defined as any intake in excess of the prescribed dose of MK-3682 or MK-8408.

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 of subjects from the time 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 of subjects that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product (or longer if dictated by local regulations) must be reported. 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 14 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 Upper Limit of Normal (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).

Additional events of clinical interest for this trial include:

1. first instance of eGFR < 30 mL/min/1.73 m2 from the initiation of study therapy through 14 days following treatment. Creatinine clearance will be evaluated as an estimated GFR (eGFR), based on the MDRD equation:

   eGFR (mL/min/1.73 m2) = 175 x (Scr, std)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if black)

   Scr, std: serum creatinine measured with a standardized assay

2. first instance of serum creatinine Grade 2 or higher (> 1.3x ULN) and elevated from baseline from the initiation of study therapy through 14 days following treatment.

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 14. The investigator's assessment of causality is required for each adverse event. Refer to Table 14 for instructions in evaluating adverse events.

Table 14 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.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

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 statistical analysis plan (sSAP) 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

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.11.

Study Design Overview	A Phase II, open-label, multicenter, multi-arm trial to study the efficacy and safety of the combination regimen of MK-3682+MK-8408 in cirrhotic or non-cirrhotic subjects with chronic HCV GT1, GT2, GT3, GT4, GT5 or GT6 infection. Subjects will receive the combination regimen of MK-3682+MK-8408 for 12 weeks. Subjects may be HCV mono-infected or HIV-co-infected, treatment-naïve or treatment-experienced with a prior interferon-based therapy.
Treatment Assignment	Approximately 250 subjects will be enrolled into six cohorts receiving MK-3682 + MK-8408 for 12 weeks based on the genotype of their HCV infections. Although within six cohorts subjects will receive the same treatment regimen, i.e., MK-3682 + MK-8408 for 12 weeks, these cohorts are designated as six "treatment arms" in the study.
Analysis Populations	Efficacy: Per Protocol (PP), modified Full Analysis Set (mFAS) and Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Proportion of subjects achieving SVR_{12} after 12 weeks of treatment
Key Secondary Endpoints	Proportion of subjects achieving SVR_{24} after 12 weeks of treatment, respectively; Proportion of subjects experiencing virologic failure at FW12 among all subjects who do not discontinue study for non-treatment-related reasons after 12 weeks of treatment, respectively.
Statistical Methods for Key Efficacy Analyses	For the primary efficacy analysis based on the PP population, the proportions of subjects achieving SVR_{12} will be estimated in each

	treatment arm, and 95% confidence intervals (CIs) for these rates will be calculated using the Clopper-Pearson method [49]. The missing data approach of Treatment-Related Discontinuation=Failure (TRD=F) will be utilized for the primary analysis. The same Clopper-Pearson method will be used to analyze all binary endpoints based on the mFAS population for each treatment arm with TRD=F as the missing data approach and based on the FAS population for each treatment arm with Missing=Failure (M=F) as the missing data approach.
Statistical Methods for Key Safety Analyses	The All-Subjects-as-Treated population will be employed for safety analyses. 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 along with the corresponding 95% CIs. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a SAE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized in the same manner.
Interim Analyses	Sentinel cohorts (i.e. first 10 subjects) in each treatment arm for GT1, GT2, GT3, and GT4 subjects will be assessed to determine the treatment duration for the main cohorts (i.e. the remaining subjects still on treatment).
Multiplicity	No multiplicity adjustment is planned for the study.
Sample Size and Power	Approximately 250 subjects will be allocated into one of the six treatment arms of combination of MK-3682 (450mg) and MK-8408 (60mg) for 12 weeks with 50 GT1-, 50 GT2-, 50 GT3-, 50 GT4-, 25 GT5- and 25 GT6-infected subjects in Arms 1, 2, 3, 4, 5 and 6, respectively Assuming a protocol violation rate of 10%, the PP population will include approximately 45 subjects in each of Arms 1, 2, 3 and 4. If the SVR_{12} rate is approximately 96% (43 successes out of 45), the exact 95% CI is (84.9%, 99.5%). The PP population will include approximately 22 subjects in Arms 5 and 6. If the SVR_{12} rate is approximately 91% (20 successes out of 22), the exact 95% CI is (70.8%, 98.9%). Detailed information is in Section 8.9.1.

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 department of the Sponsor.

This trial is being conducted as an open-label study, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. Through the course of this open-label study, efficacy and safety analyses may be performed by the Sponsor to monitor trends and facilitate programmatic decisions. In particular, when at least half of the subjects have reached FW4 and/or FW8, initial assessment of SVR_4 and/or SVR_8 may be performed.

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed in the following sections.

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} after 12 weeks of treatment.

The secondary efficacy endpoints are:

1) the proportion of subjects achieving SVR_{24} after 12 weeks of treatment.

2) the proportion of subjects experiencing virologic failure (either on-treatment failure or relapse post-treatment) at Follow-up Week 12 after 12 weeks of treatment, among all subjects who do not discontinue the study for non-treatment-related reasons.

8.4.1.2 Pharmacokinetics Endpoints

Additional details are in Section 4.2.3.3.

The primary PK endpoint for MK-3682 (and metabolites) and MK-8408 is C_{trough}.

8.4.1.3 Exploratory Endpoints

1. The emergence of RAVs to MK-3682 or MK-8408 when administered as part of a combination regimen.
2. The proportion of subjects with HCV RNA <LLOQ (either TD(u) or TND) at TW2, TW4, TW8, end of treatment, FW4, and FW8 after 12 weeks of treatment,.
3. The viral kinetics in the first 32 hours of treatment and Days 3 and 7 in the first 10 GT1-infected (two of whom are cirrhotics), 10 GT2, 10 GT3 (two of whom are cirrhotics) and up to five subjects each who are GT4, GT5 or GT6-infected who consent to participate. The collection of the viral kinetics in this subset of subjects will be used to explore the impact of early viral load decline on sustained viral response in each treatment arm as stated in the exploratory objective. The viral kinetics will be summarized, and the relationship of viral kinetics and likelihood of achieving SVR_{12} response may be explored in the future after appropriately combining subjects with viral kinetic measurements from other studies.
4. The association between genetic variation (such as IL28 genetic variation) and the clinical response to the treatment(s) administered.
5. The proportion of HIV co-infected subjects who develop HIV-1 virologic failure during protocol therapy;
6. Change from baseline in CD4+ T-cell counts in the HIV co-infected population.

8.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.3.2 and ECIs are defined in Section 7.2.3.2.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

Per Protocol (PP)

The PP population will serve as the primary population for the analysis of SVR_{12} and SVR_{24} in this study, since it provides a more accurate assessment of the virological efficacy in subjects who are reasonably compliant in this Phase 2 trial. The PP population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints. Non-virologic failures that are due to administrative reasons will be excluded. Potential violations that may result in the exclusion of a patient from the PP population include:

- The subject did not meet specific inclusion/exclusion criteria (for example, the subject is infected with a mixed GT infection or non-typeable genotype).
- The subject received concomitant medications that are prohibited due to their potential to result in a clinically significant lowering of the MK-3682 or MK-8408 concentrations (see Section 5.5 for specific details of prohibited medications). Further, any co-administered medication currently unidentified, but for which subsequent clinical DDI data indicate that co-administration with MKs leads to a clinically significant lowering of MK concentrations.
- Other violations may be identified during the course of data collection and they will be listed specifically in the CSR.

A subject with important deviations from the protocol at treatment allocation (Day 1) will be excluded from the PP population. For subjects with important deviations from the protocol as described above during the course of treatment, data obtained subsequent to the violation will be excluded from analysis.

Full Analysis Set (FAS)

The FAS population will serve as a supportive analysis of efficacy data in this study. The FAS population consists of all subjects who are assigned to a treatment arm and receive at least one dose of study treatment in this study.

Modified Full Analysis Set (mFAS)

The mFAS population will be used for the efficacy endpoints of SVR_{12} and SVR_{24} as a supportive analysis and for the endpoint of the proportion of subjects experiencing virologic failure at FW12 as a primary analysis. The mFAS population is a subset of the FAS population, with subjects excluded for study discontinuation for reasons unrelated to the treatment regimen. Examples include loss to follow-up, discontinuation from the study due to non-drug related AEs, informed consent withdrawal, and other non-virologic failures.

The final determination on the exclusion of subjects from various analysis populations will be made prior to the final database lock and will be documented in a separate memo.

Subjects will be included in the treatment arm to which they are allocated for the analysis of efficacy data using the FAS, mFAS, and PP populations. Details on the approach to handling missing data are provided in Section 8.6, Statistical Methods.

8.5.2 Safety Analysis Populations

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 allocated subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment (i.e., treatment duration, if applicable) they actually received for the analysis of safety data using the ASaT population.

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 Statistical Methods.

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 15.

Nominal p-values may be computed for some efficacy analyses as a measure of strength but no formal tests of hypotheses are planned in this study.

The analysis strategy for safety is described in Section 8.6.2.

8.6.1 Statistical Methods for Efficacy Analyses

Missing Values

A missing data point for a given study visit may be due to any one of the following reasons: a visit occurred but data were not collected or were unusable; a visit did not occur; or a 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, TD (u), and TD (q). There are 3 types of missing data handled by different approaches.

1. 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 two TND, then the missing value would be imputed as TND.

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.
3. Non-intermittent missing for reasons 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 deviation, 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 following two approaches will be used to handle non-intermittent missing data due to premature discontinuations, depending on the analytical strategy, as described in the section below and in Table 15.

1. Treatment-Related Discontinuation = Failure (TRD=F) approach: Subjects with treatment-related missing data (type #2 above) will be considered as failure; whereas the subjects who have the non-treatment-related missing value (type #3 above) and who 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.
2. Missing=Failure (M=F) approach: Subjects with any non-intermittent missing data (i.e., type #2 and #3 above) will be imputed as failures, regardless of the reason for study discontinuation.

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

Proportions of Subjects With Virologic Responses and Virologic Failures

For the primary efficacy analysis, the proportions of subjects achieving SVR_{12} after 12 weeks of treatment in each treatment arm will be provided and 95% confidence intervals for these rates will be calculated using the Clopper-Pearson method [49]. The same method will be used to analyze all binary endpoints including SVR_{24} after 12 weeks of treatment.

For all analyses conducted using the PP and mFAS populations, the missing data approach of TRD=F will be utilized. In addition, for all analyses in these two populations, a subject will be considered to have achieved a particular endpoint if the HCV RNA levels for the infection he/she had at baseline are < LLOQ. In other words, if a subject has HCV RNA levels ≥ LLOQ at a particular time point, but those RNA levels correspond to an infection that is of a different genotype and/or subtype compared to the infection detected at baseline and the baseline infection has been cleared, then the subject is considered to have achieved response for the given endpoint.

Sensitivity analyses that use the FAS population will utilize the M=F missing data approach. Also, in the FAS analyses, only subjects with HCV RNA levels < LLOQ for any type of HCV infection at a given time point will be considered to have achieved the endpoint.

To estimate the secondary efficacy endpoint of proportion of subjects experiencing virologic failure at FW12 for each treatment arm, 95% CIs for these rates will be calculated based on the mFAS analysis population using the Clopper-Pearson method [49]. The missing data approach of TRD=F described previously will be utilized for this analysis.

Table 15 includes a summary of the key efficacy analyses, and Table 16 includes a summary of the analysis populations and various criteria to assess the primary endpoint (SVR_{12} after 12 weeks of treatment) and secondary endpoints (SVR_{24} and proportion of subjects experiencing virologic failure at FW12 after 12 weeks of treatment, respectively).

Table 15 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 after 12 weeks of treatment	P	95% Confidence Interval (Clopper-Pearson)	PP	TRD=F[‡]
Proportion of subjects achieving SVR_{12} in each treatment arm after 12 weeks of treatment	S	95% Confidence Interval (Clopper-Pearson)	mFAS	TRD=F[‡]
Proportion of subjects achieving SVR_{12} in each treatment arm after 12 weeks of treatment	S	95% Confidence Interval (Clopper-Pearson)	FAS	M=F[*]
Secondary				
Proportion of subjects achieving SVR_{24} in each treatment arm after 12 weeks of treatment	P	95% Confidence Interval (Clopper-Pearson)	PP	TRD=F[‡]
Proportion of subjects achieving SVR_{24} in each treatment arm after 12 weeks of treatment	S	95% Confidence Interval (Clopper-Pearson)	mFAS	TRD=F[‡]
Proportion of subjects achieving SVR_{24} in each treatment arm after 12 weeks of treatment	S	95% Confidence Interval (Clopper-Pearson)	FAS	M=F[*]
Proportion of subjects experiencing virologic failure at FW12 in each treatment arm after 12 weeks of treatment	P	95% Confidence Interval (Clopper-Pearson)	mFAS	TRD=F[‡]

mFAS = modified Full Analysis Set
FAS = Full Analysis Set
PP = Per Protocol
[†] P=Primary approach; S=Secondary approach.
[‡] TRD=F = Treatment-Related Discontinuation=Failure.
[*] M=F = Missing=Failure.

Table 16 Analysis Populations, Criteria for Response, Non-Response, and Exclusion from Analysis Populations

Analysis Population	Criteria for Response	Criteria for Non-Response	Criteria for exclusion from analysis population
PP (Primary for SVR_{12} and SVR_{24})	HCV RNA < LLOQ for baseline infection HCV RNA ≥ LLOQ demonstrated to be due to reinfection (after clearance of baseline infection)	HCV RNA ≥ LLOQ for baseline infection*	Subject with important deviations from the protocol including subject discontinued from the study for non-treatment related reasons and other violations such as violation of I/E criteria, use of prohibited concomitant medications (see Section 8.5.1)
mFAS (Supportive for SVR_{12}, SVR_{24}; Primary for proportion of subjects experiencing virologic failure at FW12)	HCV RNA < LLOQ for baseline infection HCV RNA ≥ LLOQ demonstrated to be due to reinfection (after clearance of baseline infection)	HCV RNA ≥ LLOQ for baseline infection*	Subject discontinued from the study for non-treatment related reasons.
FAS (Supportive for SVR_{12} and SVR_{24})	HCV RNA < LLOQ	HCV RNA ≥ LLOQ	Subject did not receive at least one dose of study medication

mFAS = modified Full Analysis Set
FAS = Full Analysis Set
PP = Per Protocol
LLOQ = Lower limit of quantification
*Baseline infection: Genotype(s) and subtype(s) present at baseline based on population sequencing and genotyping assay

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

Summary statistics will be provided to describe the rates of occurrence of subject non-response, rebound, virologic breakthrough, and relapse. Definitions for subject non-response, rebound, virologic breakthrough, and relapse are in Section 4.2.3.1.1.2. Reinfection will be defined as having detectable virus of a different genotype than that detected at baseline as determined by sequencing. Those with reinfection will be considered treatment success in the mFAS and PP analyses as long as the baseline infection was achieved HCV RNA < LLOQ.

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 primary safety analysis will summarize the safety data for subjects during the treatment period plus 14 days of follow-up. The 95% CIs for the safety parameters will be estimated using the Clopper-Pearson method [49], which is a conservative exact method of providing CIs in this estimation study.

The analysis of safety parameters will follow a tiered approach (Table 17). The tiers differ with respect to the analyses that will be performed.

The first tier includes the following safety parameters or adverse experiences of special interest that will be assessed via point estimates with 95% confidence intervals for each treatment arm for GT1, GT2, GT3, GT4, GT5 and GT6 subjects and combined across genotypes after 12 weeks of treatment: (1) AEs of elevated laboratory values that are reported as ECIs described in Section 7.2.3.2; (2) at least one AE; (3) a drug-related AE; (4) an SAE; (5) a serious and drug-related AE, and (6) an AE leading to discontinuation.

All other safety parameters will be included in the second tier with point estimates to be provided for each treatment arm for GT1, GT2, GT3, GT4, GT5 and GT6 subjects and combined across genotypes after 12 weeks of treatment for the following safety parameters: specific AEs by System Organ Class (SOC), vital signs, 12-lead ECGs, and standard laboratory safety tests at time points specified in the Trial Flow Chart (Section 6.0).

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

Table 17 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, vital signs, ECG)		X

[†] Adverse Experience references refer to both Clinical and Laboratory AEs.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and other Analyses

Summaries of demographic and baseline characteristics, pharmacokinetic analyses, analyses of data from the long-term follow-up in this study (as described in Section 7.1.5.6), and analyses for the exploratory endpoints will be described in detail in the supplementary statistical analysis plan (sSAP).

8.7 Interim Analyses

Interim assessments will include the following to evaluate the need to extend the treatment duration from 12 weeks to 16 weeks. If a total of ≥3 out of the first 10 subjects in the PP population in a 12-week arm experience virologic relapse by FW4, all subjects already enrolled and on treatment in an 12- week dosing duration arm for that GT will have their treatment duration extended to 16 weeks, and no further subjects will be enrolled.

The probability of observing 3 or more subjects with virologic failure can be computed using the binomial distribution and is a function of the actual total sample size per arm (n) and the assumed proportion of virologic failure (p = 1 – true SVR rate). These probabilities

(expressed as a percent) are displayed in Table 18 for sample sizes (n) of 9 and 10 subjects and true SVR rates of 70, 75, 80, 85, and 90%.

Table 18 Probability of Observing 3 or More Subjects with Virologic Failure

	Sample Size Per Arm (n)	
True SVR Rate	9	10
0.70	53.7%	61.7%
0.75	39.9%	47.4%
0.80	26.2%	32.2%
0.85	14.1%	18.0%
0.90	5.3%	7.0%
0.95	0.8%	1.2%

8.8 Multiplicity

No multiplicity adjustment is planned for the study.

8.9 Sample Size and Power Calculations

8.9.1 Efficacy Analysis

Approximately 250 subjects will be allocated to receive treatment with MK-3682 (450mg) and MK-8408 (60mg) for 12 weeks with a target enrollment of 50 GT1-, 50 GT2-, 50 GT3-, 50 GT4-, 25 GT5- and 25 GT6-infected subjects in Arms 1, 2, 3, 4, 5 and 6, respectively. Assuming a protocol violation rate of 10%, the PP population will include approximately 45 subjects in each of Arms 1, 2, 3 and 4. The PP population will include approximately 22 subjects in Arms 5 and 6.

Table 19 below shows the two-sided 95% CIs for SVR_{12} under varying assumptions of the number of successes for the PP population. Note that these intervals are not symmetric around the point estimate.

Table 19 Two-Sided 95% Confidence Intervals for SVR_{12} (PP Population)

Number of subjects in PP population	Observed Number of Successes (%)	Two-Sided 95% Confidence Interval‡
22	21 (95.5%)	(77.2, 99.9)
	20 (90.9%)	(70.8, 98.9)
	19 (86.4%)	(65.1, 97.1)
	18 (81.8%)	(59.7, 94.8)
45	43 (95.6%)	(84.9, 99.5)
	41 (91.1%)	(78.8, 97.5)
	39 (86.7%)	(73.2, 94.9)
	37 (82.2%)	(67.9, 92.0)

‡ Based on the Clopper-Pearson method

8.9.2 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 ASaT population will include approximately 25 or 50 subjects in each of the 6 treatment arms. When combined across genotypes, the ASaT population will include approximately 250 subjects for combined treatment arm of 12 weeks. The estimate of and the upper bound of the 95% confidence interval for the underlying percentage of subjects with a specific AE given various hypothetical observed number of subjects with that specific AE within the study are provided in Table 20. These calculations are based on the exact binomial method proposed by Clopper and Pearson [49].

Table 20 Estimate of Incidence of a Specific AE and 95% Upper Confidence Bound Based on a Hypothetical Number of Subjects with that Specific AE

n	Hypothetical Number of Subjects with AE	Estimate of Incidence	95% Upper Confidence Bound†
25	0	0.0%	13.7%
	2	8.0%	26.0%
	5	20.0%	40.7%
	8	32.0%	53.5%
	10	40.0%	61.3%
50	0	0.0%	7.1%
	2	4.0%	13.7%
	4	8.0%	19.2%
	8	16.0%	29.1%
	10	20.0%	33.7%
250	0	0.0%	1.5%
	10	4.0%	7.2%
	25	10.0%	14.4%
	35	14.0%	18.9%
	50	20.0%	25.5%

†Based on the two-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934)

8.10 Subgroup Analyses and Effects of Baseline Factors

To assess the consistency of the response across various subgroups, the SVR_{12} and SVR_{24} rate and associated 95% CIs will be estimated within each category of the following baseline factors as classification variables:

- Presence or absence of baseline RAVs to any of the two classes of drugs
- Sex (female, male)
- Age (≥65, <65)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Other)
- 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
- Stage of fibrosis (non-cirrhotic, cirrhotic)
- HIV co-infection status (HCV/HIV co-infected, HCV mono-infected)
- Treatment-experienced and treatment-naïve
- For Arm 1: GT1 subjects (GT1a vs. GT1b)

The subgroup analyses will be performed within each treatment arm and based on pooled treatment arm across genotypes, as appropriate.

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 MK-3682 (450mg) + MK-8408 (60mg) 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 allocation to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from allocation to the date of the last dose of study medication.

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 by treatment group 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 dose for each study drug.

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 21.

Table 21 Product Descriptions

Product Name & Potency	Dosage Form
MK-3682, 150 mg	Tablet
MK-8408, 10 mg	Capsule

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 bottles (1 bottle of MK-3682 and 1 bottle of MK-8408) every 2 weeks during the treatment duration. Each bottle will contain a 2-week supply of study medication. 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.

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.

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 Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow 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 FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

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.

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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 7.1.3.6 – 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 PPD 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.

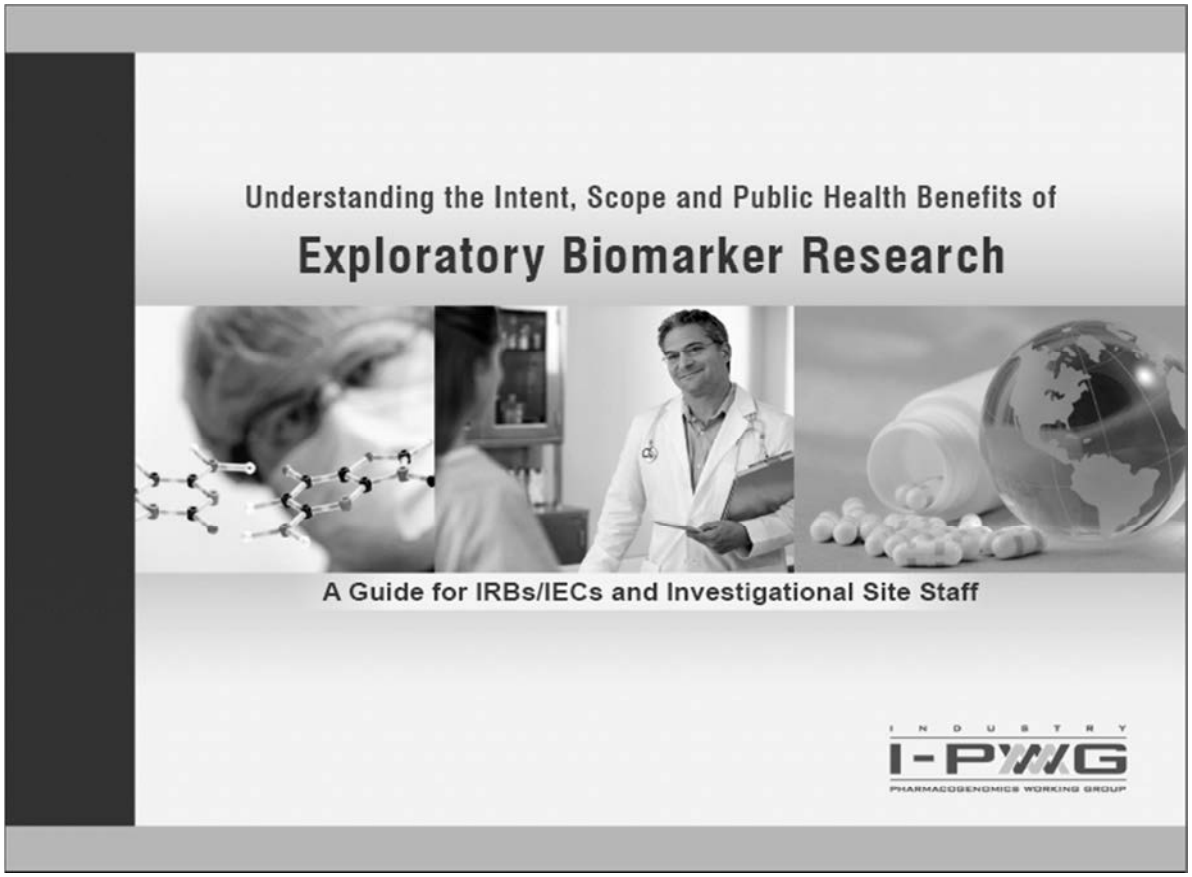
12. Questions

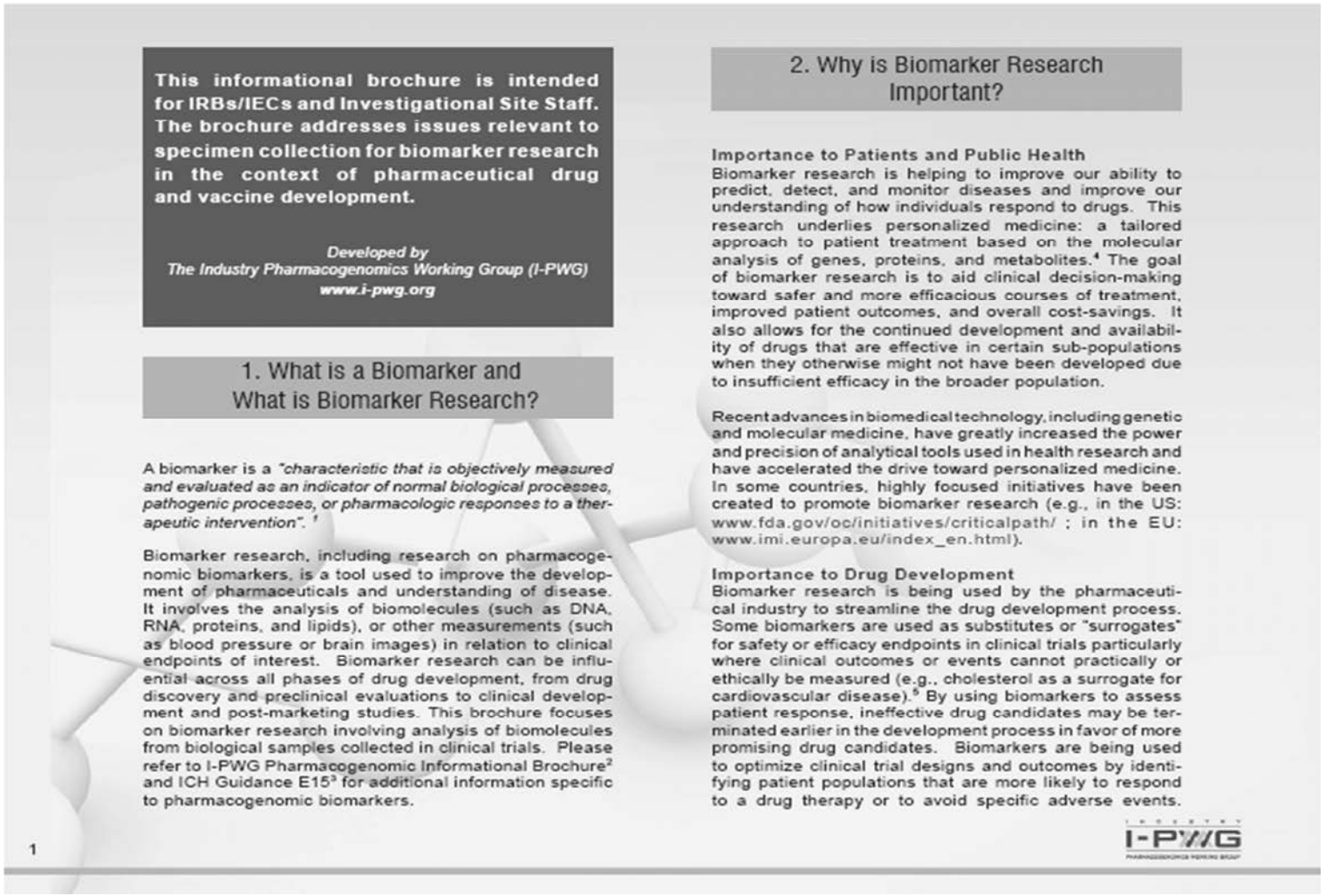
Any questions related to the future biomedical research should be e-mailed directly to PPD .

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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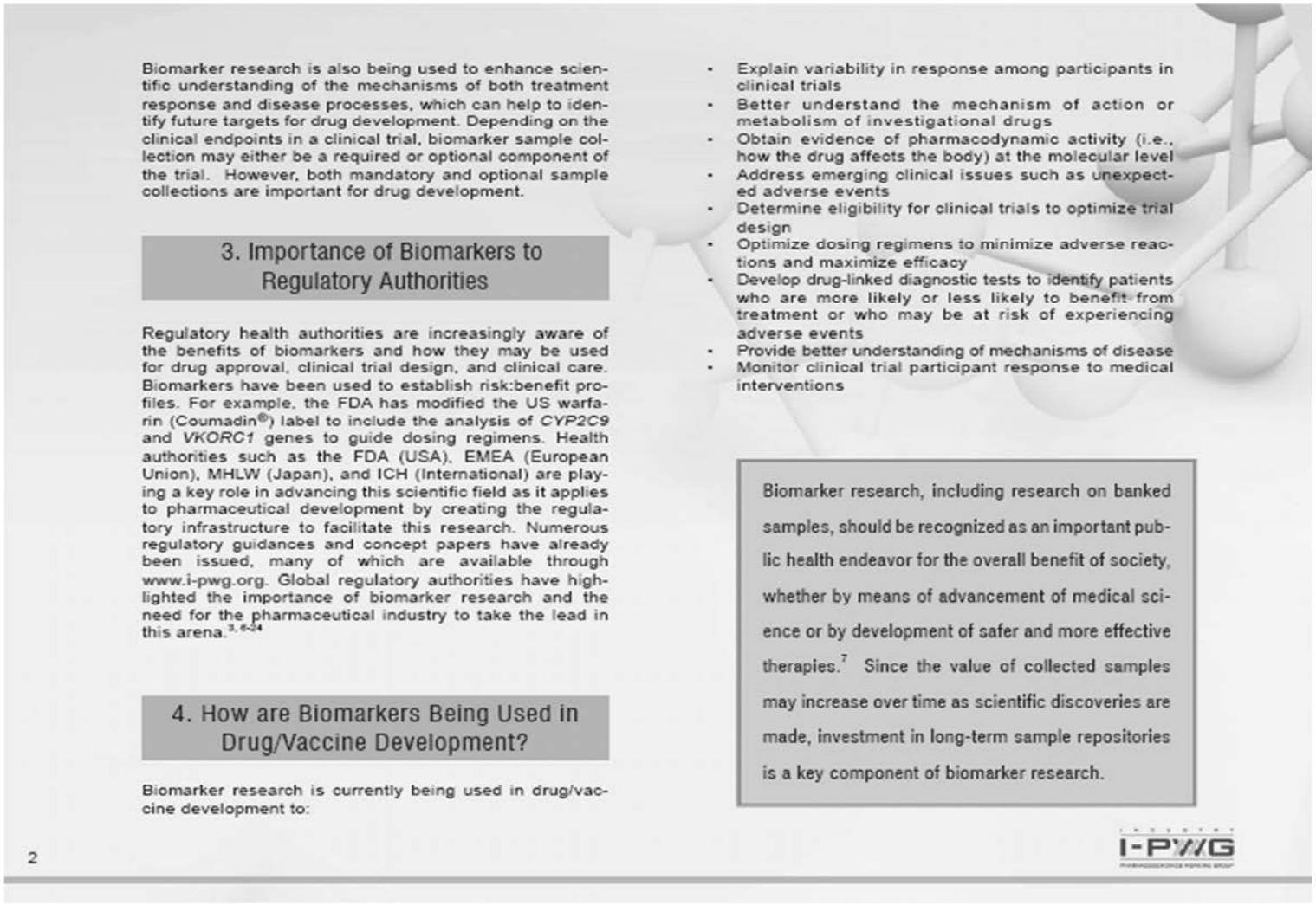
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either 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.
2
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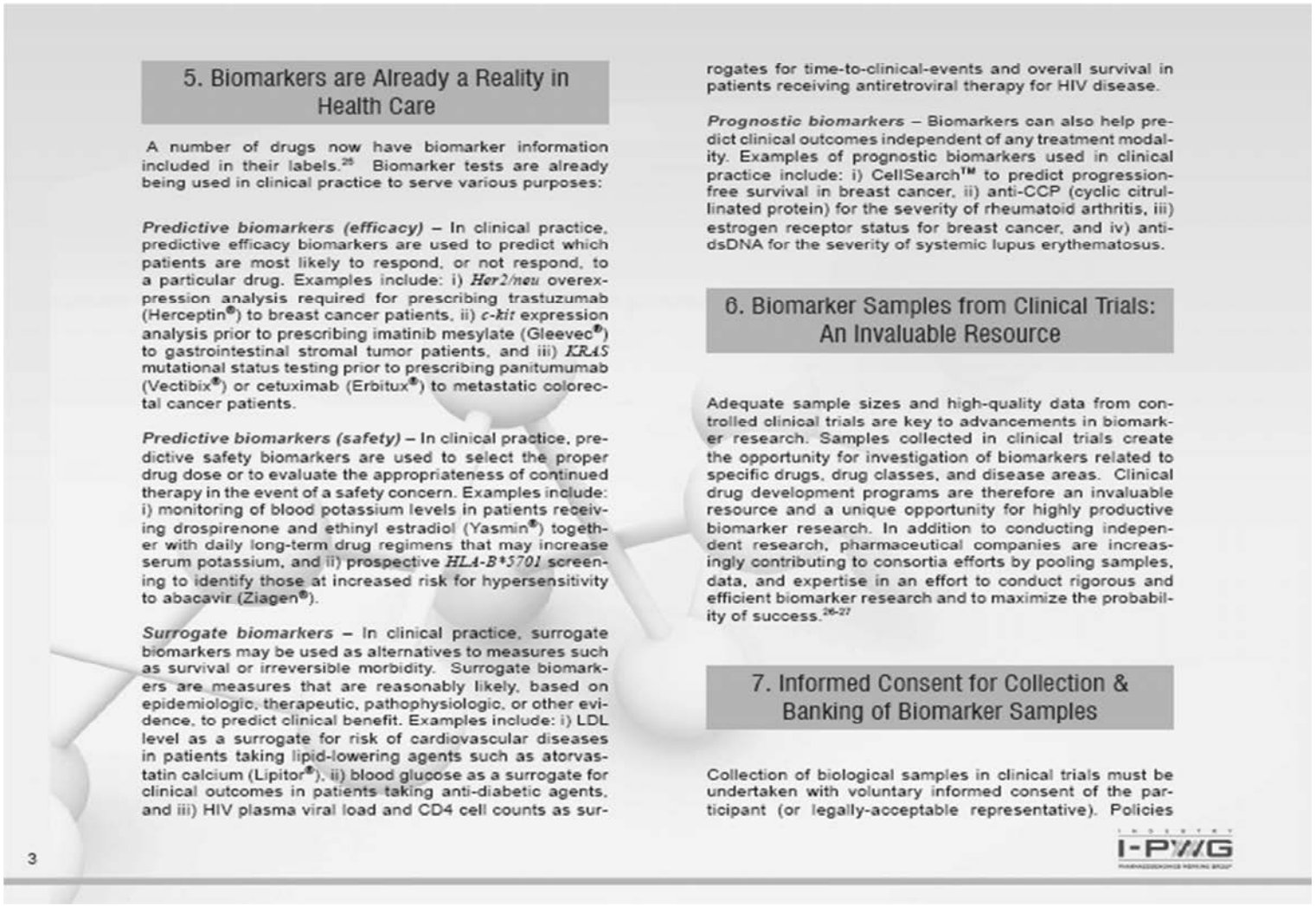

5. Biomarkers are Already a Reality in Health Care

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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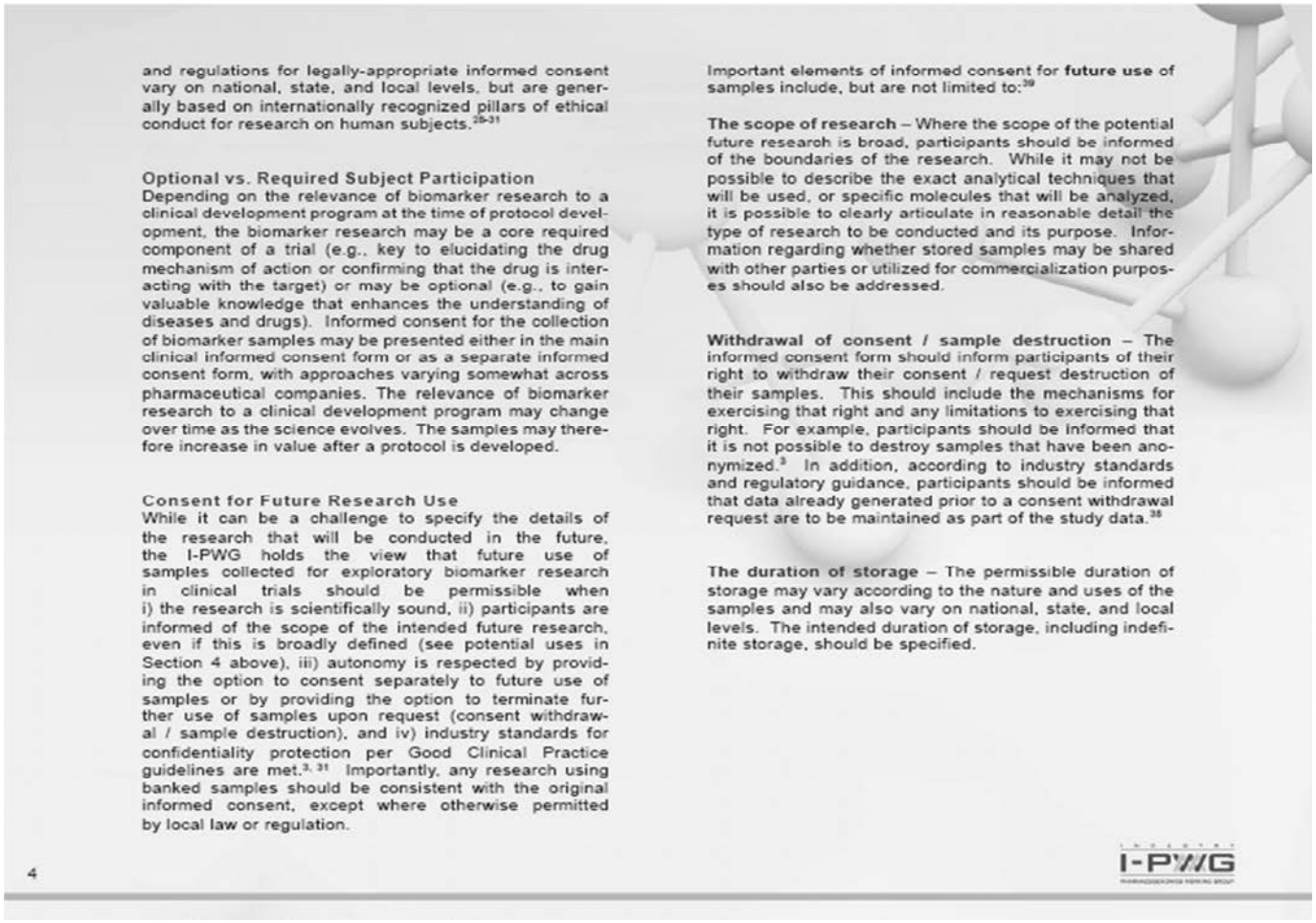

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[29-31]

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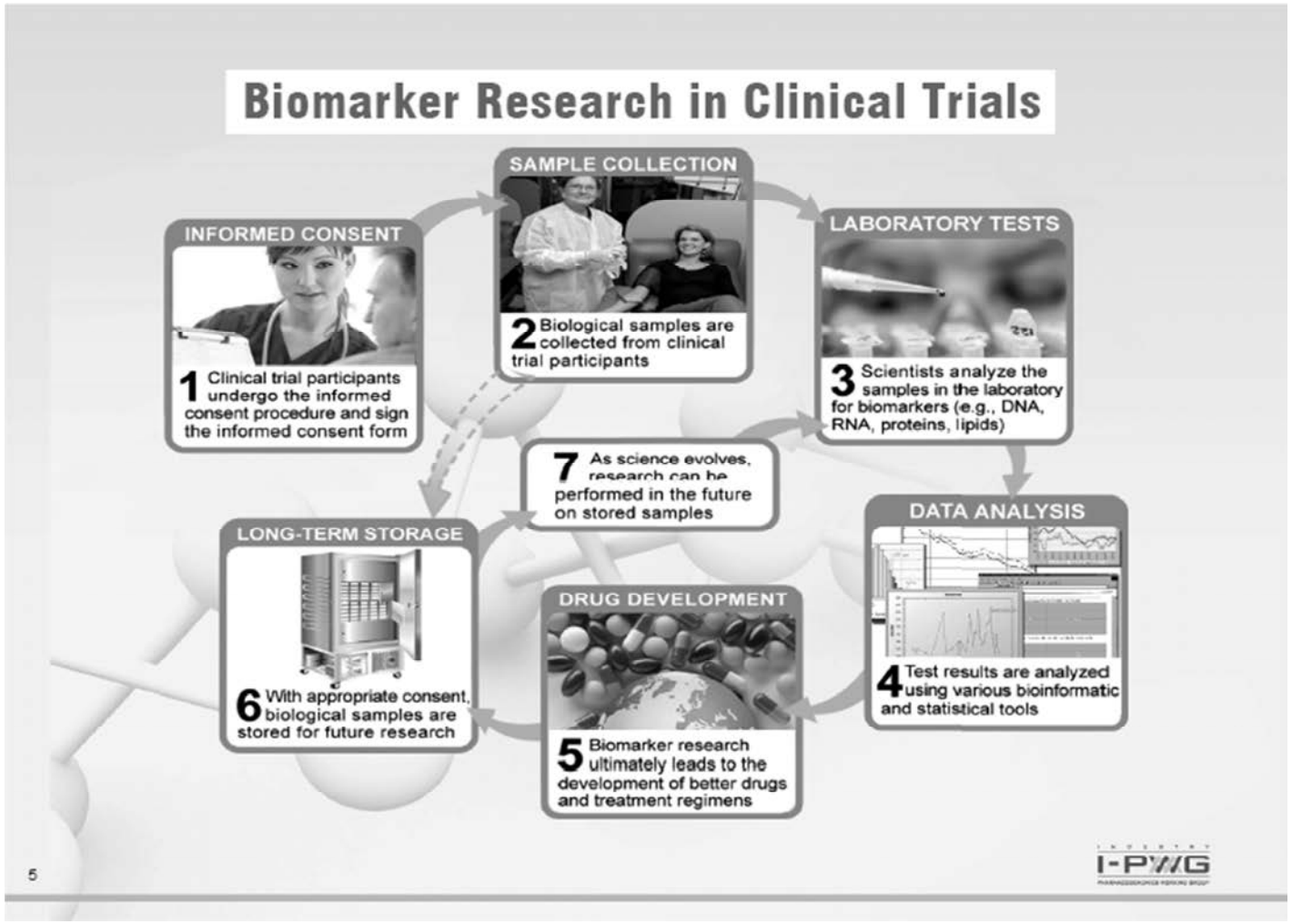
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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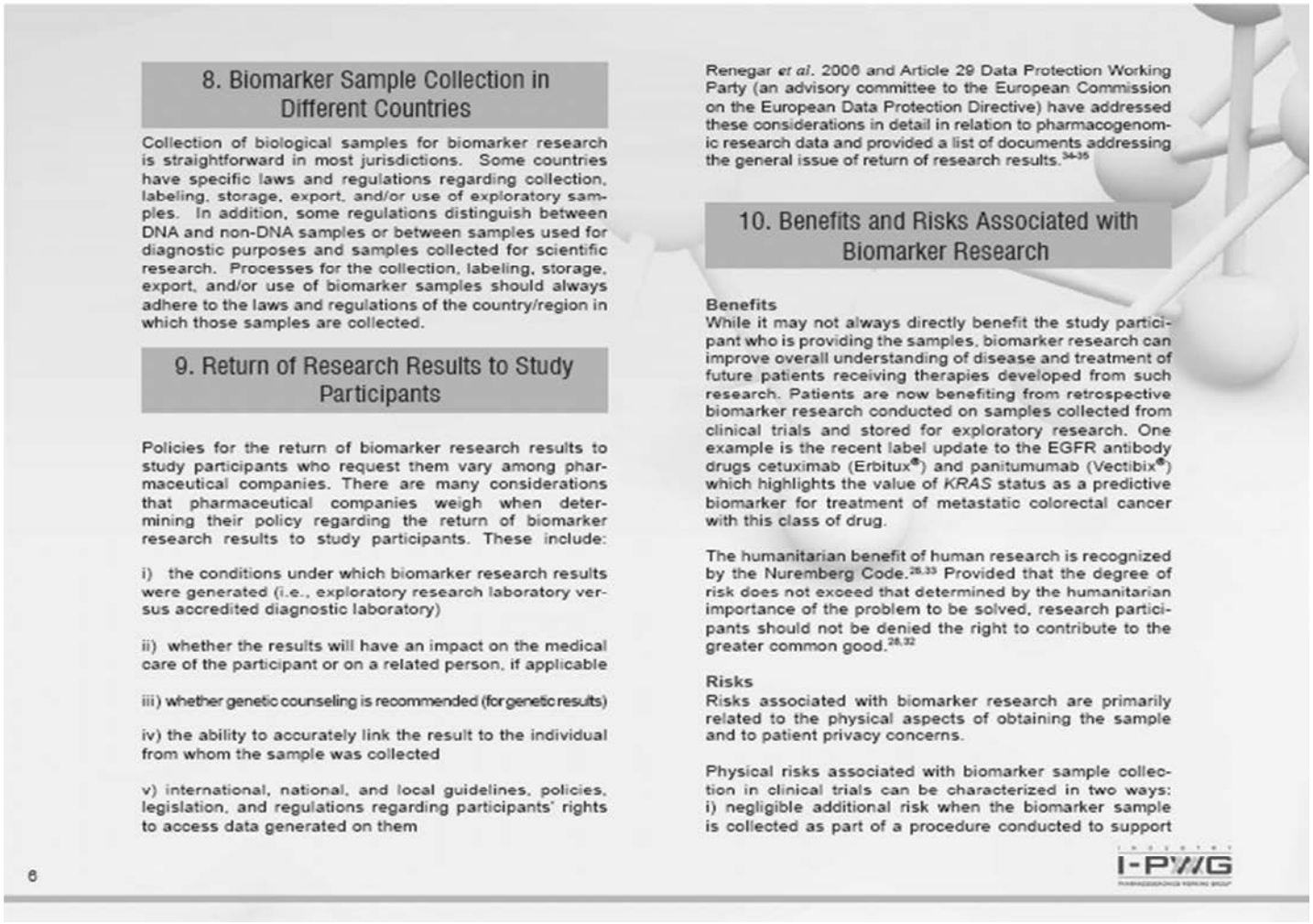

8. Biomarker Sample Collection in Different Countries

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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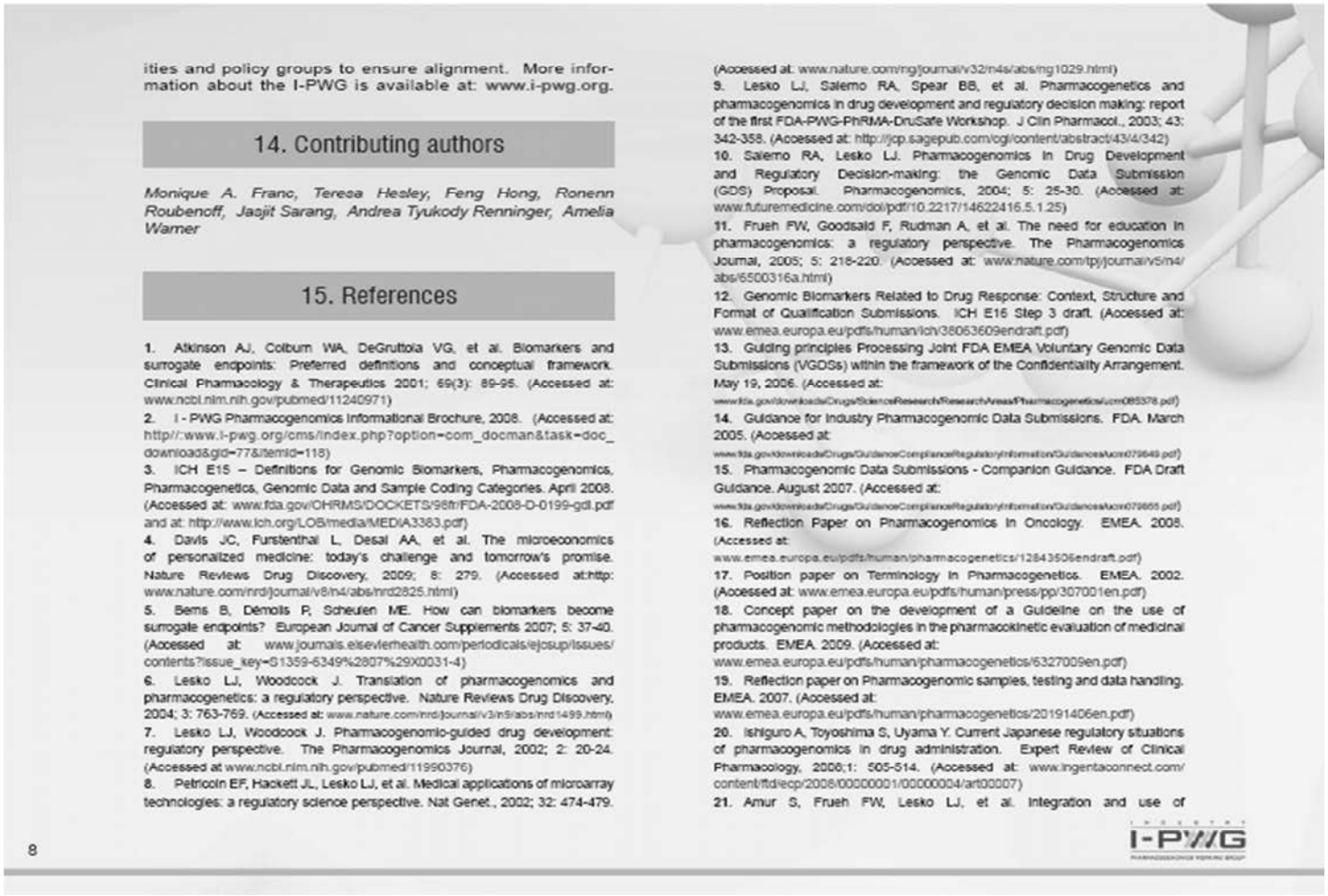

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jaajit Sarang, Andrea Tyukody Renninger, Amelia Warner

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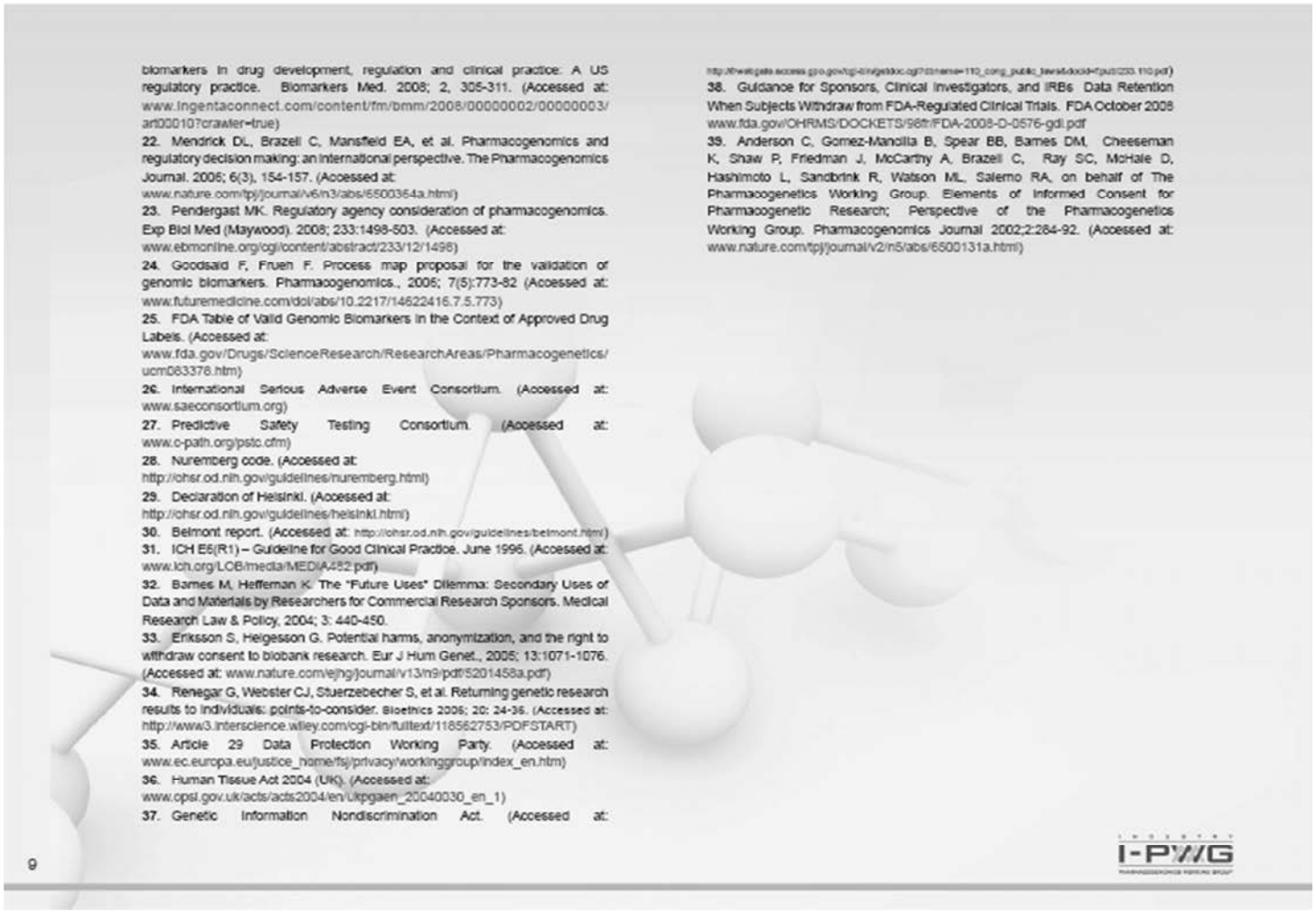

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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

	Screening	Day 1	Day 2[1]	Day 3[1]	Day 5[1]	Day 7	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14[2]	Week 16[2]	FW 4	FW 8	FW 12	FW 24	**Total Volume**
Test																			
Coagulation (PT, INR)	4.5	4.5				4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5		4.5	4.5	63
HBsAg	6																		6
HIV-1 Serology	6																		6
Chemistry	10	10				10	10	10	10	10	10	10	10	10	10	10	10	10	150
Hematology	3	3				3	3	3	3	3	3	3	3	3	3	3	3	3	45
MK-3682 PK		4		4[1]		4/16[1]	4	4/12[1]	4	4	4	4	4	4					40/68[1]
MK-8408 PK		4		4[1]		4/16[1]	4	4/12[1]	4	4	4	4	4	4					40/68[1]
HCV Genotype Determination	4																		4
HCV RNA Level	10	10/50[1]	20[1]	10[1]	10[1]	10	10	10	10	10	10	10	10	10	10	10	10	10	150/240[1]
HCV Viral Resistance and biomarkers		6													6	6	6	6	30
Blood for genetic analysis		8.5																	8.5
HIV RNA	6	6					6	6	6	6	6	6	6	6	6	6	6	6	84
HIV Viral Resistance		10																	10
CD4+ T-cell count	6	6						6		6		6	6	6	6		6	6	60
Expected Total (mL) Study Population	64	67.5	0	0	0	39.5	39.5	51.5	45.5	51.5	45.5	51.5	51.5	51.5	45.5	35	45.5	45.5	627.5/ 730.5[2]

[1] Applicable to Intensive Viral Kinetic Sub-study population only.
[2] Applicable only if the treatment duration is extended to 16 weeks.

12.5 List of Abbreviations and Definition of Terms

Term	Definition
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
APRI	Aspartate Aminotransferase to Platelet Ratio Index
ART	Antiretroviral therapy
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
C_{trough}	Trough plasma concentration
C	Cirrhotic
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CSM	Clinical Specimen Management
DAA	Direct-acting antiviral therapy
DAO	Data-As-Observed
DCV	Daclatasvir
DNA	Deoxyribonucleic Acid
EBR	Elbasvir
EC50	Half-maximal effective concentration
ECG	Electrocardiogram
ECI	Event of Clinical Interest
E/CIA	Enzyme or chemiluminescence immunoassay
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERC	Ethics committee
EU	European Union
FAS	Full analysis set
mFAS	Modified full analysis set
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FDA	Food and Drug Administration, USA
FDC	Fixed dose combination
FW	Follow-up Week
GCP	Good Clinical Practice
GT	Genotype
GZR	Grazoprevir
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
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
INR	International normalized ratio
Investigational Product	The drug, biologic, and/or device being investigated in the current trial
IRB	Institutional Review Board
LDV	Ledipasvir
LloQ	Lower limit of quantification

Term	Definition
MDRD	Modification of diet in renal disease
NC	Non-cirrhotic
OMB	Ombitasvir
PD	Pharmacodynamics
PDLC	Pre-Defined Limit of Change
PGx	Pharmacogenomics
PK	Pharmacokinetics
PP	Per-protocol
RAV	Resistance-Associated Variant
RBC	Red Blood Cell
RBV	Ribavirin
RNA	Ribonucleic Acid
Scr, std	Serum creatinine measured with a standardized assay
SAE	Serious Adverse Event
SAFE	Sequential Algorithm for Fibrosis Evaluation
sSAP	Supplemental statistical analysis plan
SOC	System Organ Class
SOF	Sofosbuvir
SOP	Standard Operating Procedure
SVR	Sustained Virologic Response
SVR_4	Sustained Virologic Response 4 weeks post-treatment
SVR_8	Sustained Virologic Response 8 weeks post-treatment
SVR_{12}	Sustained Virologic Response 12 weeks post-treatment
SVR_{24}	Sustained Virologic Response 24 weeks post-treatment
TE	Treatment Experienced
TF	Treatment Failure
TN	Treatment Naïve
TND	Target NOT Detected (HCV RNA not detected)
TD (u)	Target detected but unquantifiable
TD (q)	Target Detected, quantifiable
TRD	Treatment-Related Discontinuation
TW	Treatment Week
ULN	Upper limit of normal
USA	United States
VEL	Velpatasvir
VL	Viral load
WBC	White Blood Cell
WK	Week

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	