Observational Study Protocol

Longitudinal Assessment of Cardiovascular and Renal Health in Patients with Hepatitis-C (CARE-Hep C)

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PROTOCOL SYNOPSIS

Protocol Title	**Longitudinal Assessment of Cardiovascular and Renal Health in Patients with Hepatitis-C (CARE-Hep C)**
Indication	Increased risk of cardiac and renal dysfunction may be associated with investigational drug (BMS-986094)
Location	Approximately 16 US sites where Phase 1 and Phase 2 studies of BMS-986094 were conducted and sites where those subjects have been or will be further evaluated.
Brief Rationale	BMS-986094 is a hepatitis C virus (HCV) NS5B nucleotide analog polymerase inhibitor that was developed for the treatment of chronic HCV infection. It was administered to subjects as part of a Phase 1 multiple-dose study, as well as a 12-week study looking at combination therapy in HCV-infected subjects (Phase 2; Part A, and Part B). During follow-up, cases of cardiac and renal dysfunction were identified and subjects were discontinued on study drug. The purpose of this study will be to monitor the cardiovascular and renal health of subjects exposed to the study medication and characterize subjects' clinical status in comparison to a cohort of HCV-infected patients without exposure to BMS-986094.
Study Design	This will be a multi-center, prospective, observational study designed to assess the cardiovascular and renal health of study participants. The study will enroll up to 500 subjects, including 291 of the subjects previously exposed to BMS-986094 in the Phase 1 or Phase 2 studies of BMS-986094 and approximately 200 control subjects that include subjects with hepatitis C without exposure to BMS-986094 and those who received placebo in the BMS-986094 studies (N=50). Study participants will be followed for presence of cardiac or renal dysfunction via regularly scheduled clinical- and telephone-based assessments. The follow-up period will be up to 5 years.
Objectives	To assess the longitudinal cardiovascular and renal health of subjects exposed to BMS-986094.
Abbreviated Study Flow	Written informed consent will be obtained prior to inclusion in this study. After consent, the following will be obtained at baseline: medical history, physical examination, current medications, comprehensive metabolic panel, complete blood counts, cardiovascular, renal and hepatic biomarkers (blood and urine based), electrocardiogram (ECG), and transthoracic echocardiogram (TTE). Telephone interviews will be performed at regularly scheduled intervals, during which a health status survey will be administered and the subject will be assessed for interim changes in health status including hospitalizations and clinic visits. The subjects will visit the site for regularly scheduled visits for continued clinical assessments of cardiovascular, renal and liver abnormalities with laboratory measurements, ECGs, and TTEs. If a subject is found to have any evidence of cardiac or renal dysfunction, they will be referred to a cardiovascular or renal specialist.

	There may be a few subjects who do not have a study site and who will be followed by phone only.

Investigator Protocol Signature Page

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described. I will provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. I am aware that this protocol must be approved by the Institutional Review Board or Ethics Committee. I agree to adhere strictly to the attached protocol. I agree that clinical data entered on case report forms by me and my staff will be supplied to the DCRI and may be utilized by the DCRI in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow DCRI monitors and auditors full access to all medical records at the research facility for subjects screened or randomized in the study. I agree to provide all subjects with informed consent forms, as required by government regulations and International Conference on Harmonization guidelines.

I, the undersigned, have read and approve this protocol and agree on its content.

Principal Investigator (print name)	Site Name and Number
Principal Investigator (signature)	Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMS	Bristol Myers Squibb
BNP	B-type Natriuretic Peptide
BUN	blood urea nitrogen
CMP	comprehensive metabolic panel
Cr	creatinine
DCRI	Duke Clinical Research Institute
DCV	daclactasvir
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic Case Report Form
EC90	90% maximal effect
EDC	electronic data capture
EF	ejection fraction
HCV	hepatitis C virus
HCV RNA	hepatitis C virus ribonucleic acid
HR	heart rate
hs-cTn	high sensitivity cardiac troponin
HV	healthy volunteer
IRB	institutional review board
JVP	jugular venous pressure
LV	left ventricular
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
NS5B	nonstructural protein 5B
OSMB	Observational Study Monitoring Board
PegIFN α	pegylated interferon alpha
P-gp	P-glycoprotein
PMI	point of maximal impact
QD	once daily

RBV	ribavirin
RdRp	ribonucleic acid (RNA)-dependent RNA polymerase
RGT	response-guided therapy
RNA	ribonucleic acid
SAE	serious adverse event
SBP	systolic blood pressure
TTE	transthoracic echocardiogram

1. INTRODUCTION AND STUDY RATIONALE

1.1 Background Information

BMS-986094 (previously known as INX-08189) is a novel nucleotide analogue polymerase inhibitor developed for the treatment of chronic hepatitis C virus (HCV) infection. BMS-986094 inhibits the HCV ribonucleic acid (RNA)-dependent RNA polymerase (RdRp), encoded by nonstructural protein 5B (NS5B). In replicon cell culture systems, BMS-986094 was found to be a highly potent inhibitor of replication with a concentration resulting in 90% maximal effect (EC90) of 0.038 M against HCV genotype (GT)-1. BMS-986094 has similar potency against HCV across all genotypes tested. Combination studies using the replicon assay have suggested that BMS-986094 can be dosed with other HCV-targeting inhibitors with additive and/or synergistic responses.

BMS-986094 has been tested in healthy volunteers (HVs) and HCV-infected individuals (**Table 1**). To date, 293 subjects have received at least 1 dose of BMS-986094; of these, 291 subjects are alive. The Phase 1 studies included both HVs and HCV-infected subjects, with favorable safety profiles. In the HVs, single doses (up to 100 mg) and multiple doses (50 mg once daily [QD] for 7 days), were used, and no clinically relevant trends in adverse events (AEs), vital sign changes, electrocardiogram (ECG) changes, physical examinations, or laboratory values, have been noted. There have been no deaths in the Phase 1 studies. Two serious adverse events (SAEs) noted were not felt to be related to study drug. Two of the Phase 1 studies, BMS-986094 monotherapy (up to 200 mg QD) and BMS-986094 (up to 100 mg) in combination with Ribavirin (RBV) for 7 days, had a favorable safety profile in subjects with HCV. There were no clinically relevant trends in AEs, vital sign changes, ECG changes, physical examinations, or laboratory values. Also, there were no deaths. One subject (placebo + RBV group), who had a history of hypertension and atrial fibrillation experienced an SAE of atrial fibrillation. Another subject (BMS-986094 200 mg group) with a medical history of seizure disorder had an AE (seizure; not related to BMS-986094 by investigator assessment) that led to discontinuation of study drug. Most AEs were mild in intensity.

In the Phase 2 study (AI472003), BMS-986094 (25, 50, and 100 mg) was dosed in combination with pegylated interferon (PegIFN α) and ribavirin (RBV) for 12 weeks in Part A, at doses of 50, 100, and 200 mg with or without daclactasvir (DCV, BMS-790052) and/or RBV for 12 weeks in Part B (**Table 1**). Bristol Myers Squibb (BMS) suspended all subject dosing on August 1, 2012 after notification of a SAE of heart failure that occurred during the trial and led to the demise of the subject. Subsequently, several other potential cases of drug-related cardiac and renal toxicity were identified. At time of study discontinuation, 79 subjects in Part A of the study had completed 12 weeks of dosing with BMS-986094 (combined with PegIFN α/RBV), while 34 subjects in Part B had received 1 to 6 weeks of BMS-986094 (combined with RBV and/or daclatasvir, a first in class HCV NS5A replication complex inhibitor in Phase 3 development). The majority of subjects with evidence of cardiac and renal dysfunction are from Part B of the Phase 2 clinical trial (AI472-003). Since then, retrospective evaluation of subjects in Part A of Study AI472-003 has identified additional cases of interest. No definitive evidence of cardiac or renal dysfunction has yet been identified in the Phase 1 subjects, but comprehensive evaluations are ongoing.

Subsequent to identification of the potential cardiac and renal toxicity of BMS-986094, BMS has been working in close collaboration with the FDA and clinical study investigators to conduct comprehensive safety assessments and close follow-up of all BMS-986094 study subjects. Duke Clinical Research Institute (DCRI) is creating an observational registry of subjects who were exposed to BMS-986094 for purposes of understanding the incidence of cardiac and renal dysfunction associated with the study drug and facilitating referral to subspecialists when appropriate.

Table 1 Phase 1 and Phase 2 Studies of BMS-986094

Study Treatments	Study Number	Phase 1 Studies	Active Treatment Subjects	Placebo Subjects
Single dose: 094 alone	**INH-189-001**	(1 day dosing; 3, 9, 25, 50, 100 mg of 094) ➢ Single Ascending Dose Study in Healthy Volunteers	32	10
Multiple dose: 094 (or PBO) alone, or 094 (or PBO) + RBV	**INH-189-002**	(7 days dosing; 9, 25, 50, 100 mg of 094) ➢ 7-Day Multiple Dose Study in GT1 HCV Subjects (5 cohorts: 094 monotherapy/ 2 cohorts: 094 in combination with RBV)	56	14
Multiple dose: 094 (or PBO) alone, or 094 (or PBO) + Victrelis (boceprevir)	**INH-189-004**	(5 - 8 days dosing; 50 mg of 094) ➢ Drug-Drug Interaction Study with Victrelis (boceprevir) in Healthy Volunteers	28	4
Day 0: Single dose 094; Days 6 – 11: verapamil HCl ER QD Day 12: Single dose 094 + verapamil HCl ER	**INH-189-005**	(single sequence: 094 50 mg x1 on Day 0, verapamil 240 mg QD on Days 6 - 11, then 094 + verapamil on Day 12) ➢ Drug-Drug interaction Study with P-gp inhibitor (verapamil ER) in Healthy Volunteers	24	0
Multiple dose: 094 alone or 094 + RBV	**INH-189-006**	(7 days dosing; 100, 200 mg of 094) ➢ 7 Day Multiple Dose Study in GT1 HCV Subjects (Additional work on dose response and effect of food)	40	10
Study Treatments	**Study Number**	**PHASE 2**	**Active Treatment Subjects**	**Placebo Subjects**
Multiple dose: 094 added on to pegIFNα + RBV	**INH-189-003/ A1472003**	(**Part A, GT 2/3** – 12 weeks, RGT + 25, 50, or 100 mg of 094) (**Part B, GT 2/3 and GT1**– dosing interrupted; 50, 100, 200 mg of 094) ➢ Efficacy Study in GT 2/3 and GT1 Treatment-Naïve Subjects	79 34	12 0

Definitions: PBO=placebo; mg=milligrams; 094=BMS-986094; GT1=HCV genotype 1; HCV=hepatitis C virus; RBV=ribavirin; P-gp=P-glycoprotein; ER=extended release; RGT=response-guided therapy; GT2/3=HCV genotype 2 or 3.

1.2 Study Rationale

To describe cardiovascular and renal health among subjects exposed to BMS-986094 and to monitor their liver disease, a registry is being created that will enroll and follow subjects who were exposed to BMS-986094 and still alive, as well as subjects either with known HCV infection who have no history of exposure to BMS-986094, including subjects in the prior studies who received placebo. The aims of this study are to (1) perform frequent evaluations for the detection of cardiac and renal dysfunction and (2) arrange for appropriate referral if evidence of dysfunction is found. This study will include those subjects within the Phase 1 trials with varying amounts of exposure (N=180), as well as both Part A (79) and Part B (34) of the Phase 2 trial.

These evaluations will consist of a phone call screening for symptoms, physician visits for medical histories, physical examinations, laboratory testing, ECGs, and transthoracic echocardiograms (TTEs) to screen for evidence of cardiac dysfunction. Referrals to cardiologists and nephrologists at pre-specified centers may be facilitated, based on these results.

2. OBJECTIVES

2.1 Primary Objective

To describe the longitudinal cardiovascular and renal health of subjects exposed to BMS-986094.

Overall Risk Benefit

No study drug(s) will be administered and no experimental procedures will be performed as part of this study. The procedures performed in this protocol will include clinical screens for signs and symptoms of cardiovascular or renal disease, and medical procedures that include phlebotomy, ECGs, and TTEs. These procedures have minimal associated risk, and will inform subjects of their cardiovascular status; thus, the benefits of inclusion into the study are expected to outweigh the risks.

3. STUDY DESIGN AND DURATION

3.1 Overview of Study Design

This will be a multi-center, prospective, observational study designed to assess the cardiovascular and renal health of previous BMS-986094 study participants who received study drug in comparison to HCV infected subjects without exposure to BMS-986094, as well as participants in the prior studies who received placebo (some of whom were healthy controls). Study participants will be followed via regularly scheduled site and telephone based assessments. The follow-up period will be up to 5 years from last inclusion in the registry. This registry is designed to be observational and the clinical management of these subjects remains the responsibility of the usual care physician.

The schedule of assessments is summarized in **Table 2**.

3.2 Study Population

3.2.1 Inclusion Criteria

Subjects will be enrolled based on prior enrollment in the BMS-986094 studies or treatment-naïve HCV subjects with no known cardiovascular abnormalities.

1. All Subjects must give informed consent prior to participation in the study.
2. Subject participated in the Phase 1 or Phase 2 trials with BMS-986094 (including placebo arm)

OR

3. Subject with known hepatitis C (Control)
   - **a.** No previous exposure to BMS-986094
   - b. Treatment naive at study entry (No prior hepatitis C treatment experience at the time of enrollment, including but not limited to: standard interferon, pegylated interferon, ribavirin, boceprevir, telaprevir, or other experimental drugs for hepatitis C).

3.2.2 Exclusion Criteria

1. For subjects who participated in the Phase 1 or Phase 2 trials with BMS-986094, there are no exclusion criteria
2. For the control group of subjects without exposure to BMS-986094, the following exclusion criteria, based on clinically available data, apply:
   - **a.** Signs or symptoms of decompensated liver disease such as variceal bleeding, ascites, hepatic encephalopathy, active jaundice defined by an indirect bilirubin >2, ALT or AST laboratory values ≥ 10 times the upper limit of normal, or other evidence of decompensated liver disease or hepatocellular carcinoma
   - **b.** Chronic liver disease other than HCV not limited to Hepatitis B virus (positive test for HBsAg), hemochromatosis, auto-immune hepatitis, alcoholic liver disease or non-alcoholic fatty liver disease
   - **c.** History of liver transplantation

d. Co-infection with HIV (positive test for anti-HIV Ab)
e. Prior history of cardiomyopathy (ejection fraction ≤ 50%) or history of heart failure
f. Signs or symptoms of decompensated heart failure or
g. Prior history of coronary artery disease, acute myocardial infarction or coronary artery revascularization (percutaneous or coronary artery bypass grafting)

3.2.3 Discontinuation of Subjects from Study

Subjects will discontinue from the study if they withdraw informed consent or are unable to freely provide consent.

4. STUDY PROCEDURES

4.1 Summary of Procedures

Subjects who participated in a Phase 1 or Phase 2 trial with BMS-986094 and received study drug as well as control subjects that include patients with known hepatitis C (see criteria above) and those in the placebo arms of the prior trials will be contacted and asked to give informed consent for enrollment into the study. Subjects will be enrolled based on existing medical records or clinical site data that supports the inclusion/exclusion criteria. If subjects meet exclusion criteria after enrollment (e.g. ALT or AST laboratory values ≥ 10 times the upper limit of normal) upon receipt of baseline labs, the subject may stay in the study. Once consented, all subjects will complete an initial study visit at Day 1 at the study site. Relevant previous data collected during the subject's participation in a Phase 1 or 2 study of BMS-986094 may be transferred from BMS to DCRI and entered into the study database, as needed. All enrollees will undergo baseline assessment (see **section 4.3.1**). Schedule of assessments for subjects in either arm of the registry will be identical (See **Table** 2).

Subjects who do not have a study site, due to relocation or for other reason(s), may be followed by phone only by the DCRI Call Center according to Table 3. The other procedures outlined in this protocol do not apply to this subset of subjects.

4.2 Schedule of Assessments

The schedule of assessments is shown in **Table** 2. Decisions about modification to schedule of assessments will be made during annual Observational Study Monitoring Board (OSMB) meetings and review of data. The proposed duration of follow up, from time of initial assessment by a physician, is up to 5 years for each subject enrolled in the registry.

Table 2 Schedule of Assessments

	Years 1-2										Years 3-5				
Assessment	**Baseline**	**3mo**	**6mo**	**9mo**	**12mo**	**15mo**	**18mo**	**21mo**	**24mo**	**30mo**	**36mo**	**42mo**	**48mo**	**54mo**	**60mo**
Informed Consent	X														
Medical History & Physical Exam (including vital signs)	X		X		X		X		X		X		X		X
Phone Call to Subject for Health Status Survey		X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*
Medications	X		X		X		X		X		X		X		X
CMP, CBC	X		X		X		X		X		X		X		X
FibroSURE	X														
Liver Disease Assessment**	X				X				X		X		X		X
Cardiac and Renal Biomarkers***	X		X		X		X		X		X		X		X
ECG	X		X		X		X		X		X		X		X
Transthoracic Echo	X		X		X		X		X		X		X		X

*** DCRI call center may contact subject by phone call if he/she misses in-person assessment.**

**** Liver Disease Assessment includes: HCV RNA, PT/PTT/INR**

***** See Section 4.7 for details**

Table 3 Schedule of Assessments for Subject Follow-up by DCRI Call Center Only (subjects without a site)

	Years 1-2										Years 3-5				
Assessment	**Baseline**	**3mo**	**6mo**	**9mo**	**12mo**	**15mo**	**18mo**	**21mo**	**24mo**	**30mo**	**36mo**	**42mo**	**48mo**	**54mo**	**60mo**
Informed Consent[a]	X														
Phone Call to Subject for Health Status Survey	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collection of Medical Records[b]	X		X		X		X		X		X	X	X	X	X

[a] **Informed consent forms will be mailed to the subjects, discussed over the phone with the DCRI Call Center, and signed and mailed back to the DCRI Call Center.**

[b] **Collection of medical records if subject signs medical release form that will be mailed with the informed consent form. Preferably the treating physician should send the medical records to DCRI Call Center including records of physical exams, medications, lab results, safety event information, results of any cardiac procedures and any other relevant information. Medical records may also be collected at other times should phone interviews trigger the need for supporting information.**

4.3 Study Site Visits

4.3.1 Baseline (Initial Visit)

Baseline assessments will occur at the time of first study visit (Day 1) and will include:

- Comprehensive physical examination, including vital signs
- Past Medical History
- Cardiovascular, renal and hepatic concomitant medications
- Local Laboratory Tests: comprehensive metabolic panel (CMP), complete blood count (CBC)
- Central Laboratory Tests
  - Liver Disease Assessment: HCV RNA, PT/PTT/INR (see Section 4.7)
  - FibroSURE
  - Cardiac Biomarkers (see Section 4.7)
  - Renal Biomarkers (see Section 4.7)
- Electrocardiogram (ECG)
- Transthoracic echocardiogram (TTE)

4.3.2 Follow-up

Follow up in-person visits will occur according to year of study and will include:

- Focused physical examination
- Interval medical history
- Changes in cardiac, renal, and hepatic medications
- Local Laboratory Tests: comprehensive metabolic panel (CMP), complete blood count (CBC)
- Central Laboratory Tests
  - Liver Disease Assessment: HCV RNA, PT/PTT/ INR (see Section 4.7) Note: Liver Disease Assessment only conducted at months 12, 24, 36, 48 and 60.
  - Cardiac Biomarkers (see Section 4.7)
  - Renal Biomarkers (see Section 4.7)
- Electrocardiogram (ECG)
- Transthoracic echocardiogram (TTE)

Telephone visits will include:

- Interval medical history
- Health Status Survey

4.4 Telephone Interviews with Health Status Survey

All subjects will be contacted by telephone for structured interviews by trained DCRI personnel who are part of the DCRI Outcomes call center to provide surveillance for any cardiovascular and renal symptoms. Questions will be included to allow for discerning between cardiac or pulmonary etiology of symptoms. The telephone visits will be done at standard intervals between site visits. During years 1-2, the telephone visits will be done every 6 months and during years 3-5, the telephone visits will be done every 12 months. Telephone visits will also be used to contact subjects if they miss scheduled clinic

visits. Any change in subject's cardiovascular or renal health status will result in notification of the site investigator and the medical monitor. The primary responsibility for following up on the notification will lie with the site investigator. In the future, if yet known symptoms or organ toxicities that may be related to BMS-986094 are identified, health status surveys might be modified to include relevant questions.

4.5 History and Physical

All study participants will undergo medical history and physical exam on initial visit, along with a review of current medications related to cardiovascular, renal or hepatic disease. During subsequent visits, subjects will undergo a focused history and physical exam that aims to uncover signs and symptoms of cardiac or renal dysfunction. Additionally, changes in medications, as well as recent hospitalizations, specifically for cardiovascular or renal causes will be documented. Subjects will be queried about any significant changes in clinical care such as need for dialysis or episodes of acute kidney injury. In the future, if yet known symptoms or organ toxicities that may be related to BMS-986094 come to light, history and physicals might be modified to include relevant questions.

4.6 Routine Laboratory Assessments

Study participants will have laboratory values checked at the local laboratory according to the schedule of assessments. These will include comprehensive metabolic panel and complete blood count. Any clinical interventions indicated by laboratory results will be at the discretion of the site PI. In all circumstances, the sites will be responsible for modifying clinical care based on these results per standard of care. HCV RNA, PT/PTT/INR, and FibroSURE will be done at a central laboratory (see Section 4.7). The DCRI coordinating PI and co-Investigators will be available for follow up and consultation with the site as needed.

4.7 Biomarker Assessment

Subjects enrolled in the study will be asked to provide blood and urine samples for biomarker analyses as well as storage for future use. These will be performed at a central laboratory. Ongoing testing of biomarkers will include those that may indicate pathophysiological changes to cardiovascular, renal, or hepatic status and include:

Cardiovascular biomarkers:

- B-type natriuretic peptide [BNP]
- High sensitivity cardiac troponin (hs-cTn)
- Storage for future use (optional)

Renal Biomarkers:

- Cystatin-C
- Albumin
- Storage for future use (optional)

Hepatic Biomarkers:

- FibroSURE (baseline only)
- PT/PTT/ INR
- Hepatitis C RNA

A central laboratory will provide all labels, tubes and requisitions necessary for the above mentioned biomarkers and samples for storage. Sites will have access to all central laboratory results and will also be informed of certain abnormal values. In all circumstances, the sites will be responsible for modifying clinical care based on these results per standard of care. The DCRI coordinating PI and co-Investigators will be available for follow up and consultation with the site as needed.

If the subject consents, blood and urine samples will be collected and stored for future use.

4.8 Electrocardiograms and Echocardiograms

Resting transthoracic two-dimensional (2-D) and Doppler echocardiograms and static 12-lead ECGs will be performed according to the schedule of assessments in **Table** 2.

Protocols and procedures for acquiring and transmitting detailed resting, transthoracic 2-D, and Doppler echocardiogram and standard 12-lead ECG image acquisition are included in the study manual of procedures. Each study site will identify their preferred echocardiography laboratory. The echo lab, as well as the study site, will be trained and qualified before any subject may be enrolled. The echo lab will be expected to maintain minimal quality standards throughout the study. Importantly, images and ECGs should be acquired using only subject study number, initials, and date of study. Sites will transfer study echocardiograms on a CD-ROM or DVD and paper ECGs via courier to DCRI Imaging Core Laboratory (Core Lab), within three business days.

All study echocardiograms and ECGs will be independently analyzed by the DCRI Imaging Core Lab. Upon arrival in the Core Lab, echocardiograms will be de-identified by removing or masking all protected health information on the images and will undergo quality review with feedback returned to the site's clinical echo lab.

Echocardiograms will be analyzed for systolic and diastolic left ventricular (LV) function, anatomic measurement of LV and atrial volumes, valvular regurgitation, wall thickness, wall motion score and LV mass index. Electrocardiograms will also undergo quality review and feedback and will be analyzed for rhythm, intervals, and evidence of ischemia or hypertrophy.

All echocardiograms and ECGs will be analyzed by the core lab within 7 business days of resolution of any queries. A report will be communicated to the study site within one business day of physician interpretation.

In addition sites will identify any clinical echocardiograms or ECGs obtained during the study period with significantly abnormal findings (evidence of cardiac function, as defined below) and send the images and/or ECG to the DCRI Imaging Core Lab, along with the clinical report (site interpretation).

4.9 Evidence of Cardiac Dysfunction

Any of the following findings will be considered potentially indicative of cardiac dysfunction/heart failure and would prompt referral to cardiovascular specialist, closer follow-up, and/or hospitalization. The decision will be left to the discretion of the treating physician. Abnormal responses to the cardiovascular questionnaire or testing will be evaluated by the medical monitor at DCRI and results reported to the site for further evaluation as clinically indicated.

a) Abnormalities on history and physical exam may include:
   - Symptoms of cardiovascular disease or heart failure such as increasing shortness of breath, chest pain, fatigue, orthopnea, paroxysmal nocturnal dyspnea, syncope or presyncope.
   - Physical exam findings concerning for heart failure such as hypotension (systolic blood pressure [SBP] < 90 mm Hg), tachycardia (heart rate [HR] > 100 bpm), elevated jugular venous pressure (JVP > 10 cm H_20 while sitting upright), rales or crackles on pulmonary exam, extra heart sounds (S3 or S4), murmurs (holosystolic or diastolic murmur), lower extremity edema, decreased distal pulses, and cool extremities.
   - Hospitalization for any cardiac cause.

b) Abnormalities in laboratory values (defined as >upper limit of normal defined by laboratory in subjects with normal baseline values and >25% change from previous visit in those with abnormal values):
   - Evidence of myocardial injury, as noted by abnormal level of hs-cTn.
   - Evidence of myocardial stress, as noted by abnormal levels of BNP.

c) Abnormalities on ECG:
   - Evidence of any ECG abnormalities new from baseline (or most recent) ECG.

d) Abnormalities on TTE:
   - Evidence of new myocardial dysfunction on imaging, defined as left ventricular ejection fraction (LVEF) < 50% or any regional wall motion abnormality.
   - New moderate or greater valvular regurgitation.
   - New moderate or greater chamber enlargement.

4.10 Evidence of Renal Dysfunction

Any of the following findings will be considered potentially indicative of renal dysfunction failure and would prompt referral to renal specialist, closer follow-up, and/or hospitalization. The decision will be left to the discretion of the usual care physician.

a) Abnormalities on history and physical exam:

   - Symptoms of renal failure such as reduce urine output, flank plain, rash, abdominal pain.
   - Hospitalization for any renal cause.

b) Abnormalities in laboratory values (defined as >upper limit of normal defined by laboratory in subjects with normal baseline values and >25% change from previous visit in those with abnormal values):

- Evidence of renal dysfunction, as noted by significant increases in BUN, Cr, cystatin C.
- Abnormal urine albumin level as defined as a spot urine albumin creatinine ratio >300 mg/g.

4.11 Hospitalizations

Hospitalization is defined as inpatient admission to a hospital for a period greater than 24 hours. All hospitalizations, regardless of whether it was associated with a reportable SAE (defined as an SAE related to cardiac or renal dysfunction or resulting in death), will be collected and recorded on the appropriate module of the eCRF. If the primary diagnosis of admission was a reportable SAE, the SAE eCRF will also be completed. Hospitalizations not associated with a reportable SAE should not be reported as an SAE.

4.12 Subject Withdrawal

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care. In the case of subject withdrawal, the investigator will discuss with the subject the most appropriate way to terminate study participation to ensure the subject's health. All efforts will be made to complete and report the observations as thoroughly as possible up to the date of study withdrawal. Subjects will have the right to return to the study after withdrawal at any time.

4.13 DCRI Call Center Follow-up only

Subjects who do not have a study site may be followed by the call center through phone follow-up. These subjects must have a local treating physician in order to be followed by the call center. They will continue to receive all care and treatment from their local healthcare provider. The call center staff will provide a brief explanation regarding the observational/telephone only follow up to the subject and then mail the consent form, medical release form and patient contact information sheet to the subject. Approximately one week later, the subject will be called and the consent form and medical release form will be reviewed over the phone. If the subject agrees to participate, they will sign the forms and send back to the call center. Once the documents are received; the call center will request medical records from the subject's healthcare provider to assist in establishing baseline medical history. Any data that can be extrapolated from these records will be entered into the database.

This small group of subjects will have telephone visits done at 3 month intervals during years 1-2 and every 6 months during years 3-5. The subjects will be informed of any changes in their health that warrant seeking advice and care from their local physician. It will be explained that the survey in no way takes the place of the need for physician follow up and does not provide any treatment if there can be no site follow up. The survey will be for data collection only in these cases.

5. SAFETY EVALUATIONS

5.1 Definitions

5.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered an investigational intervention and which does not necessarily have a causal relationship with study treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with use of the study drug, whether or not considered related to an investigational intervention.

5.1.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that may result in any of the following outcomes:

- Death
- Is life-threatening
- In-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes.

5.2 Collection of Adverse Events

This is a long-term observational, non-interventional study. For this study, non-serious AEs will not be collected.

5.3 Assessment of Serious Adverse Events

As this is a long-term observational, non-interventional study, temporal association with the use of study drug, as referenced in 5.1.1, is not applicable. Collection, evaluation, and reporting of SAEs will be limited to SAEs related to cardiac or renal dysfunction and SAEs resulting in death.

5.3.1 Assessment of SAE Severity

The determination of SAE severity rests on medical judgment of a medically-qualified investigator. The severity of SAEs will be graded using the following definitions:

- **Mild:** awareness of sign, symptom, or event, but easily tolerated;
- **Moderate:** discomfort enough to cause interference with usual activity and may warrant intervention;

- **Severe:** incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

5.3.2 SAE Collection and reporting

Collection, evaluation, and reporting of SAEs will be limited to SAEs related to cardiac and renal dysfunction and SAEs resulting in death. In the future, if symptoms or organ toxicities that may be related to BMS-986094 are identified, the reporting of SAEs may change. SAEs will be collected and recorded on the SAE page of the eCRF from the signing of informed consent to the end of the follow-up period.

SAEs related to cardiac dysfunction, renal dysfunction and SAEs resulting in death, regardless of causality, must be reported by the investigator or qualified designee as soon as they become aware of the event. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF. DCRI Safety Surveillance will be notified of SAEs via an electronic data capture (EDC)-generated email. DCRI Safety Surveillance will perform a review of all SAE forms to verify that all sections are complete and consistent and will issue queries on the SAE panel in the EDC system for incomplete or inaccurate information. If the eCRF system is temporarily unavailable, the event should be reported via a paper back-up SAE form to the DCRI Safety Surveillance. Upon return of the availability of the EDC system, the SAE information must be entered into the eCRF. DCRI will send reported SAEs to BMS in aggregate approximately every 6 months.

Additional details regarding the collection and reporting of SAEs will be documented in the safety plan.

5.3.3 Laboratory Test Abnormalities

For laboratory test abnormalities that meet the definition of an SAE and that required the subject to receive specific corrective therapy, the clinical diagnosis, rather than the laboratory term, will be used by the reporting investigator (e.g., elevated BUN and creatinine versus renal insufficiency/renal failure).

5.3.4 Follow-up of SAEs

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. The investigator will follow all events until resolution, stabilization or the event is otherwise explained. DCRI Safety Surveillance will follow all SAEs until resolution/stabilization/until the event is otherwise explained/ or until the last subject completes the final follow-up, whichever occurs first. DCRI will report SAEs to BMS in aggregate approximately every 6 months.

5.4 Expedited events/ SUSAR

BMS will evaluate the SAE data for regulatory reporting criteria and will be responsible for submission to the appropriate authorities.

6. STATISTICAL CONSIDERATIONS

6.1 Population for Analysis

This will be a multi-center, prospective, observational study designed to assess study participants for signs and symptoms of cardiovascular and renal dysfunction. The study will aim to enroll 291 of the subjects originally treated in Phase 1 and Phase 2 of the BMS-986094 studies, as well as approximately 200 unexposed subjects with HCV and subjects enrolled in the original trial but who received placebo, who will serve as controls.

6.2 Statistical Analysis

As the primary objective, measures of cardiovascular and renal dysfunction among subjects exposed to BMS-986094 will be summarized in aggregate and will include exploration of trends observed during the long term follow-up period. Primary measures will include subject symptoms, findings on physical examination, laboratory measures including a range of biomarkers related to cardiac and renal dysfunction, ECG changes, development of new cardiovascular-related adverse events, and findings from transthoracic echocardiography.

As a secondary objective, the evolution and status of underlying liver disease in this population will also be summarized. This will include trends in HCV RNA as well as changes in clinical laboratory measures of liver function and coagulation observed through the follow-up period.

Statistical analyses will be presented largely as descriptive statistics as well as tabular and graphic formats reflecting trends over time. In addition to the data elements gathered during this study of long term safety surveillance, study data collected as part of the initial study enrollment and treatment will be combined and analyzed when appropriate for a thorough analysis of the study population.

Further analytic detail will be provided in a statistical analysis plan. The plan will describe the planned statistical analyses for presentation to the Observational Study Monitoring Board (OSMB) as well as at the conclusion of the study. Agreement to the statistical analysis plan will be required prior to distribution of study results.

6.3 Primary Objective and Endpoints

The primary endpoint will be to assess incidence of cardiovascular and renal dysfunction among subjects exposed to BMS-986094 and compare with a similar population of HCV subjects who were not exposed to BMS-986094. Recommendations will be made for referral to appropriate cardiovascular and renal specialists when concerning abnormalities are identified. Statistical analysis will focus on collected data related to prior and ongoing subject assessments and performing descriptive statistics on the cohort at regular intervals.

7. STUDY RESPONSIBILITIES

7.1 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to DCRI. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

7.2 Training

Prior to the start of enrollment, the physician investigators and study coordinators at each site will be trained on the clinical protocol and data collection procedures, including how to use the eCRF system. Initial investigator and coordinator training will occur with an InForm trainer and hands-on database interaction. This trainer will present slides, demonstrate key InForm functionality and guide attendees through practice exercises. Follow-up training and training for new study personnel will be conducted by DCRI personnel who will present slides, demonstrate the system and guide attendees through practice exercises using on-line web-based teleconferences.

7.3 Monitoring

The DCRI will ensure that data collection is being handled properly, will provide in service training, and address questions from site investigators and coordinators. Data quality and completeness will be reviewed by the DCRI team on a regular and ongoing basis, and any issues noted will be addressed with the site. Monitoring visits will be completed as described in the Clinical Monitoring Plan.

7.4 Remote Monitoring and Site Training

The study will be monitored remotely by representatives of the DCRI or its designee according to the prospective clinical monitoring plan for real-time monitoring of compliance with study protocol.

7.1 Audits/Inspections

DCRI Quality Assurance personnel, or a qualified designee, may conduct audits at the study site. Audits will include, but not be limited to: audit trail of data handling and processes, presence of required documents, the informed consent process, and comparison of case report forms/database with source documents. The investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed. Regulatory authorities may also audit an investigator during or after the study. The site investigator should contact the Principal Investigator(s) as well as their IRB/IEC, immediately if this occurs, and must fully cooperate with governmental (e.g. FDA) audits conducted at a reasonable time in a reasonable manner.

7.2 Clinical Study Report and Subsequent Publications

DCRI will reserve the right to publish manuscripts or abstracts arising from this study after approval by BMS prior to publication or presentation and will adhere to BMS's publication requirements. Study records will be maintained by the site investigators until told otherwise by DCRI and/or BMS.

7.3 Study Closeout

Upon completion of the study (defined by all subjects have completed all follow-up visits, all CRFs are complete, and all queries have been resolved), DCRI will notify the site of closeout and a study closeout visit will be performed. All CRFs will be collected and any unused study materials will be destroyed. The DCRI monitor will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include: discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

8. ETHICAL CONSIDERATIONS

8.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with DCRI standard operating procedures. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996, (which incorporate the principles of the Declaration of Helsinki)
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

8.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form, and other information for subjects must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to the Coordinating Center (DCRI) before study initiation. The name and occupation of the chairman and the members of the IRB/IEC must be supplied to the Coordinating Center if this information is released by IRB/IEC. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

8.3 Informed Consent

The investigator or designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the subject was unable to sign the form. No subject can enter the study before his/her informed consent has been obtained. The informed consent forms are part of the protocol, and must be submitted by the investigator with it for IRB/IEC approval. The Coordinating Center will supply proposed informed consent forms, which comply with regulatory requirements, and are considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Coordinating Center before submission to the IRB/IEC, and a copy of the approved version must be provided to the Coordinating Center after IRB/IEC approval.

8.4 Observational Study Monitoring Board

An independent Observational Study Monitoring Board (OSMB) will review accumulating data at regular intervals (at least every 12 months) and provide a recommendation to the study leadership following each planned review. The primary focus of the board will be to identify unanticipated safety concerns or trends felt to warrant action prior to the expected termination of the registry, as well as to make recommendations regarding the frequency of subject assessment. Procedural details of the structure and function, frequency of meetings, and data planned for review will be included in an OSMB charter, which will be finalized prior to the first OSMB review meeting.

8.5 Study Documentation

Study documentation includes all case report forms, data correction forms, source documents, monitoring logs and appointment schedules, Sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approval, approved and signed subject consent forms, Statement of Investigator form, and clinical supplies receipts and distribution records).

The investigator will prepare and maintain complete and accurate study 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 study, promptly complete all original case report forms and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with DCRI.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to DCRI by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of DCRI or responsible government agencies as required by law.

The investigator agrees to promptly take any reasonable steps that are requested by DCRI as a result of an audit to cure deficiencies in the study documentation and case report forms.

8.6 Source Documentation

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original certified document. All laboratory source documents will be available for all normal and abnormal results.

Regulations require that Investigators maintain information in the study subject's medical records which corroborate data collected on the CRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by DCRI monitors, or designees, and/or regulatory inspectors:

- Medical history/physical condition of the study subject prior to involvement in the study sufficient to verify protocol entry criteria.
- Medical record documenting that informed consent was obtained for the subject's participation in the study.
- Dated and signed notes for each subject visit including results of examinations.
- Notations on abnormal lab results and their resolution.
- Dated printouts or reports of special assessments, (e.g., ECG reports).
- Description of adverse events and follow-up of the adverse events (minimally event description, severity, onset date, duration, relation to study treatment, outcome and treatment for adverse event).
- Notes regarding concomitant medications taken during the study (including start and stop dates).
- Subject's condition upon completion of or withdrawal from the study.

8.7 Modification of the Protocol

The Investigator must not implement changes of the protocol without prior written agreement by the DCRI and prior review and documented approval/favorable agreement by the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., changes in research personnel or change in phone numbers).

8.8 Deviations to the Protocol

Deviations to the protocol must be documented and reported to the DCRI. Protocol deviations should be reported to the site IRB per their guidelines.