Clinical Study Protocol

Study Title: Effect of Ledipasvir and Sofosbuvir on Proteinuria and Estimated Glomerular Filtration Rate in Patients with Early Stage (1-3) Hepatitis C Associated Chronic Kidney Disease

Sponsor: Massachusetts General Hospital

Indication: Hepatitis C Virus infection and Hepatitis C related chronic kidney disease

Study Principle Investigator:

Dr. Raymond Chung
Phone: 617-724-7562
Fax: 617-724-1091

Dr. Meghan Sise
Phone: 617-643-3948
Fax: 617-724-1122

Study Center: Massachusetts General Hospital

Number of Subjects planned: 24

Duration of treatment: Subjects will be treated for 12 or 24 weeks

Protocol Version/Date: Amendment 3 30 March 2017

PROTOCOL AMENDMENT SUMMARY OF CHANGES
PROTOCOL AMENDMENT 3

Study IN-US-337-1777
Effect of Ledipasvir and Sofosbuvir on Proteinuria and Estimated Glomerular Filtration Rate in Patients with Early Stage (1-3) Hepatitis C Associated Chronic Kidney Disease

Original Protocol Date:	04 May 2015
Amendment 1 Date:	10 June 2015
Amendment 2 Date:	12 August 2015
Amendment 3 Date:	30 March 2017

Rationale	Herein is a summary of the major changes made to the protocol Amendment 2 dated 12 August 2015 and reflected in Amendment 3 dated 30 March 2017: • Clarification of Inclusion/Exclusion Criteria (including those with resected and cured thyroid cancer and excluding those that are HBV surface antigen positive. • Addition of 24 weeks of therapy where this is standard of care per AASLD guidelines. • Addition of Appendix 2, study schedule of events for 24 week regimen

Section:	Appendices: Appendix 2
Original Text:	*None*
Revised Text:	Inclusion of Appendix 2
Rationale:	Schedule of events included for clarification of study specific procedures and sample collection for 24 week regimen.

1.1 Background

Infection with hepatitis C virus (HCV) affects an estimated 180 million people, and is a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Chronic kidney disease (CKD) is common in Hepatitis C virus (HCV) infected individuals. Between 55-85% of HCV infected patients have glomerular disease on kidney biopsy.[1, 2] HCV is associated with accelerated rates of progression to end-stage renal disease (ESRD).[3] Adjusted analyses show that patients with CKD and HCV are 34-68% more likely to develop ESRD than non-infected patients.[4-6]

Historically, those with CKD who achieve SVR with interferon and ribavirin experience improvement in estimated glomerular filtration rate (eGFR).[7-9] The new era of HCV therapy allows us to test the reversibility of the association between HCV infection and CKD. Our preliminary data in cryoglobulinemia shows that patients treated with sofosbuvir-based regimens who achieve SVR had a > 70% reduction in proteinuria and a 12.6mL/min improvement in eGFR (Sise ME, in preparation). Reduction in proteinuria is an important component of the definition of clinical remission in treatment of glomerular diseases and an accepted surrogate for CKD progression [10, 11].

For the past 3 decades, treatment of chronic infection has centered on weekly injections of pegylated interferon in conjunction with weight-based dosing of oral ribavirin, and has been successful in achieving a sustained virologic response (SVR, defined as an undetectable HCV RNA level 24 weeks after the cessation of antiviral therapy) in 40 to 50% of patients with genotype 1[12-14]. More recently, the molecular characterization of the life cycle of HCV has led to the development of directly acting antiviral agents that have resulted in improved efficacy and tolerability. The fixed-dose combination ledipasvir-sofosbuvir was recently approved by the Food and Drug Administration (FDA) for the treatment of patients with HCV genotype 1 infection, and is associated with SVR rates of 93% to 95% among treatment-naïve patients receiving 8-12 weeks of therapy. [15] Ledipasvir is a potent inhibitor of NS5A, a viral protein that plays an important role in viral replication, assembly, and secretion; and sofosbuvir is a nucleotide analog inhibitor of NS5B polymerase, which mediates HCV RNA replication.

Safety

Safety data on this combination tablet have been reported in manufacturers labeling. Fatigue was reported by 13-18%, headache by 11-17%. Less frequent events reported include Insomnia (3-6%), Nausea (6-9%), diarrhea (3-7%), increased serum lipase (3x ULN ≤ 3%), hyperbilirubinemia 1.5x ULN ≤3% . The most frequent (greater than or equal to 15% overall) adverse events (AEs) on treatment were fatigue, headache and nausea.

Rationale for the current study

We hypothesize that patients with early stage (1-3) CKD caused by HCV infection will have significantly improved proteinuria and eGFR after viral eradication with LDV/SOF. This trial data will serve as the basis to support further study of LDV/SOF in patients with early CKD. Slowing progression of CKD is a critical goal, as the increasing incidence and prevalence of advanced CKD and ESRD places significant health burden on patients and tremendous costs on our health-care system.

2. Study Design

This prospective single-arm intervention trial assesses the effect of ledipasvir and sofosbuvir on kidney function in patients with hepatitis-C associated chronic kidney disease. There will be a screening period of up to 60 days to assess subject eligibility to enroll in the trial including confirmation of proteinuria (>300mg/gram creatinine). Two urinary measurements above 300mg/gram creatinine will be required within 30 days of the first dose of ledipasvir and sofosbuvir. There will be a treatment phase lasting 12 or 24 weeks and a follow-up phase lasting 12 months (from treatment initiation).

Treatment phase: An open label, non-randomized, 12 (or 24) week treatment period performed in 24 subjects assessing efficacy, safety and tolerability of a combination tablet of ledipasvir dosed at 90mg per day and sofosbuvir dose at 400mg per day. If an SAE (Grade 3 or greater event) occurs it will be reported within 24 hours to the IRB and the DSMB. The data safety monitoring committee will meet once during the treatment trial or sooner if needed based on SAE.

Study Procedures

Screening
Screening will begin with obtaining the subjects signed informed consent and will occur up to 60 days prior to the first dosing of study drug at Day 1. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead ECG, prior/concomitant medication review, urine collection for pregnancy test (females < 50), blood collection for chemistry and hematology and coagulation and cystatin C, urine collection for urine protein, albumin, B2 microglobulin and creatinine measurement. Presence of cirrhosis will be determined by Fibroscan obtained during the screening period if a fibroscan or liver biopsy has not been performed in the last 12 months. Cirrhosis will be defined as a liver biopsy showing cirrhosis or a Fibroscan score of > 13 kPa. For patients with cirrhosis, liver imaging (either ultrasound or CT scan) will be required within 6 months of the baseline visit to access for hepatocellular carcinoma (HCC). Patients with HCC will be excluded.

Patients will be eligible if blood pressure is < 140/90 and stable at both screening visits. If blood pressure is above goal, patients will undergo medication adjustments by treating clinician and are eligible to be re-screened once blood pressure is < 140/90 for two months. Baseline protein-to-creatinine ratio will be measured twice prior to dosing Day 1 to assess subject baseline proteinuria prior to beginning treatment. More than 50% variability in baseline proteinuria measurements will results in a third measurement and the average of all measures will be used as study baseline. Two health-related quality of life questionnaires (SF-36, Fatigue Index (FACIT-F)) will be administered at baseline.

Treatment
All treatment and follow-up visits will take place at MGH. Treatment will occur over 84 days (12 weeks). Subjects meeting eligibility will begin ledipasvir 90mg/sofosbuvir 400mg oral combination tablet once daily with or without food. For missed dose(s) of study medication, subjects will be instructed to take the missed dose of study mediation as soon as possible during the same day. Subjects will be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

Subjects will undergo visits at 2 weeks, 4 weeks, 8 weeks and 12 weeks (24 weeks as well for those on 24 weeks of treatment) on treatment. Safety and efficacy assessments will occur on an outpatient basis including physical exam, vital signs and weight, 12-lead ECG, details of adverse events related to procedures, details of concomitant medications, collection of blood samples (for chemistry, hematology, cystatin C) and urine samples (pregnancy for females < 50, and proteinuria, microalbuminuria, creatinine, and B2 microglobulin measurements). Fasting blood samples will be taken at four timepoints (Baseline Visit, Week 8 Visit, SVR12 visit, and 1 year follow-up visit) in order to assess insulin resistance, a major contributor to kidney disease risk. Patients will be asked to fast after midnight **for at least 8 hours** on the days of the four fasting visits. Health related quality of life questionnaires will be administered at monthly intervals on treatment and during all follow-up visits. The subject should read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire. Study schedule of events can be found in Appendix 1.

Study drug dosing will continue in the absence of toxicity warranting discontinuation of therapy for a total of 12 or 24 weeks.

Treatment Discontinuation Criteria

1. Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subjects best interest
2. Pregnancy of a female subject
3. Significant protocol violation
4. Subject request to discontinue for any reason
5. Discontinuation of the study at the request of Gilead, regulatory agency, or an IRB or DSMB
6. Virologic failure – defined below

Virologic Response-Based Stopping Criteria:
The following on-treatment virologic response-based treatment stopping criteria will be utilized:

- Confirmed HCV RNA ≥ LLOW after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 log10 increase from nadir
- HCV RNA ≥ LLOQ through 8 weeks of treatment

Confirmation should be performed as soon as possible and no later than 2 weeks after initial observation indicating a virologic failure during the on-treatment phase.

All subjects who terminate treatment early will complete an early termination visit and will complete all remaining follow-up visits with study measurements on the normal timeline as below.

Study Visit Timeline
Baseline/Screening – Two visits in 60 days prior to treatment Day 1. Baseline visit fasting
Two weeks on Treatment – W2
Four weeks on Treatment – W4
Eight weeks on Treatment – W8 (Fasting Visit)
Twelve weeks on Treatment – W12
Twenty four weeks on treatment- W24

Four weeks Post Treatment – W16 (or W36)
Twelve weeks Post Treatment – W24 (or W44) (Fasting visit)
Twenty-four weeks Post Treatment – W36 (or W56)
1 Year follow-up – W-52 (or W64) (Fasting visit)

Subject Remuneration:
All subjects will participate in two screening visits to confirm study eligibility. Subjects will be paid $10 for the initial screening visits. Subjects will be given a parking voucher for each additional study visit completed.

3. Subject Population

Number of subjects: Twenty-four patients will be enrolled in this study.

Inclusion Criteria

1. The subject has signed the written informed consent
2. Male or female ≥ 18 year of age
3. HCV genotype 1 or 4 with ribonucleic acid (HCV RNA) greater than 1000IU/mL, determined by HCV RNA polymerase chain reaction Roche COBAS TaqMan quantitative assay. If historic result is older than 24 months, genotype will be repeated at screening visit 1.
4. Initial diagnosis of proteinuric chronic kidney disease occurred < 7 years prior to completion of screening
5. Women of childbearing potential (i.e. women who have not undergone hysterectomy or bilateral oophorectomy, or no medically documented ovarian failure, and are ≤ 50 years of age) must agree to 1 medically approved contraceptive measures and have their partners agree to an additional barrier method of contraception for the duration of the study and for 4 weeks after the last administration of the study drug. Women of childbearing potential must not rely on hormone-containing contraceptive as a form of birth control during the study but may use. An intrauterine device, female barrier methods with cervical cap or diaphragm with spermicidal agent, tubal sterilization, or vasectomy in male partners.
6. Male subjects must agree to consistently and correctly use a condom during heterosexual intercourse and avoid sperm donation for the duration of this study and for 90 days after the last dose of ledipasvir and sofosbuvir. Additionally, if their female partner is of childbearing potential (as defined above), their partner must agree to use either 1 of the non-hormonal methods of birth control listed above or a hormone-containing contraceptive for 90 days after last study drug date. Hormone-containing contraceptive options for partners include implants of levonorgestrel, injectable progresterone, oral contraceptives, contraceptive vaginal ring, or transdermal contraceptive pat
7. Adequate organ function defined as follows platelets ≥ 50 x 10^9/L; hemoglobin ≥ 9 g/dL, estimated glomerular filtration rate ≥ 30mL/min/1.73m^2 as estimated by CKD-Epi equation.
8. Liver imaging to exclude HCC is required within 6 months in any patient with cirrhosis.

9. Has ≥ 300mg/g creatinine proteinuria on average of two urine samples obtained within 30 days of starting ledipasvir and sofosbuvir.

Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study

1. History of evidence of clinically significant disorder other than hepatitis C virus infection or clinically significant laboratory finding that in the investigator's judgment would pose a risk to subject safety, interfere with study procedures, or prevent completion of the study.
2. Pregnant or lactating female
3. Uncontrolled depression or psychiatric disease interfering with the ability to comply with the study procedures or complete the study
4. History or presence of any form of cancer within 3 years prior to enrollment, with the exception of excised basal cell or squamous cell carcinoma of the skin, stage 0 or 1 melanoma, resected and cured thyroid cancer, or cervical carcinoma in site or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis.
5. Experience life-threatening cryoglobulinemic vasculitis requiring initiation of rituximab, steroids or plasmapheresis.
6. Concomitant use of cimetidine, trimethoprim or other drugs which can increase tubular creatinine reabsorption
7. Uncontrolled cardiovascular or pulmonary disease
8. Uncontrolled hypertension
9. Known HIV infection. HIV testing will be performed at screening visit 1 if no result is available within 6 months of informed consent.
10. Known hypersensitivity to ledipasvir or sofosbuvir
11. Prior HCV treatment failure using a medication in the NS5A inhibitor class
12. Individuals who are taking the following medications and require continuation of the medications during the proposed study period will be excluded, given known interactions with ledipasvir-sofosbuvir: Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifabutin, rifampin, isoniazid, rifapentine, rosuvastatin, digoxin, modenafinil, and St. John's wort, milk thistle, Echinacea and amiodarone. Subjects with a history of gastric reflux who are taking proton pump inhibotors (PPI) will be asked to switch to an H2 blocker with prescribing physician approval. If subject continues to have reflux refractory to H2 blocker, 20mg of the PPI omeprazole can be given concurrently with study drug.
13. Having an alternate explanation of chronic kidney disease, including:
    a) Diabetic kidney disease, either by biopsy findings or duration of uncontrolled diabetes > 8 years without serologic evidence of immune-complex related kidney disease
    b) Chronic hypertensive nephropathy without proteinuria
    c) Lupus nephritis
    d) Multiple myeloma
    e) Obesity related proteinuria, BMI > 35

f) Ongoing nephrotoxic medication use, including NSAIDS
g) Polycystic kidney disease
h) Kidney biopsy showing an alternate explanation for chronic kidney disease

14. Positive hepatitis B surface antigen test.

4. Biostatistical Analysis

Primary endpoints of the trial include:

Primary Endpoint:
1. The percent change in proteinuria [Time Frame: 24 weeks]

Secondary Endpoints(s):
1. Mean change in eGFR as measured by creatinine and cystatin C-based estimating equation. [Time Frame: 24 weeks]
2. The proportion of patients achieving at least a 25% reduction in proteinuria [Time Frame: 24 weeks]
3. Mean time (in weeks) to maximum reduction in proteinuria [Time Frame: 24 weeks]
4. Mean change in renal function (creatinine based eGFR) over 12 months [Time Frame: 52 weeks]
5. Change in urinary **β-**2microglobulin levels before and after therapy with ledipasvir and sofosbuvir [Time Frame: 24 weeks]

Other endpoints of interest
Additional evaluations will include health related quality of life endpoints

Demographics
Demographic and baseline characteristics will be summarized using standard descriptive methods by treatment group and overall. Demographic data will include sex, self-identified race/ethnicity, and age. Baseline characteristic data will include body mass index, HCV RNA level, genotype HCV infection.

Primary efficacy
During the study period, we will measures proteinuria by a ratio of the urine protein to urine creatinine on spot urine samples. We will measure serum chemistries, serum cystatin C and urinary B-2microglobulin levels over the course of the study. These measurements will take place at every study visit.

Safety
Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized

5. Risks and Discomforts

Since patients will need blood draws for each visit,

Side effects for patients taking ledipasvir-sofosbuvir include the side effects associated with the FDA-approved product, including fatigue, headaches, nausea, diarrhea, and insomnia.

Participants will fill out study questionnaires, which capture information such as age, gender, race/ethnicity, quality of life, sources patient laboratory data (including HCV, HBV and HIV status). All information will be kept confidential and will remain in a locked cabinet, and only study personnel will have access to the data.

For standard diagnostic ultrasounds there are no known harmful effects on humans. For standard diagnostic CT scan, there is a risk of radiation exposure. The total amount of radiation exposure patients may encounter is about 6.5 milliSieverts (mSv).

6. Potential Benefits

A potential benefit to subjects is that they may be cured from HCV infection by receiving ledipasvir-sofosbuvir treatment as recommended by the FDA. Current data suggest the likelihood of cure is greater than 90%.

Another potential benefit is improvement in kidney function and liver function with successful cure of HCV.

7. Costs

Routine healthcare costs will be covered by the participants insurance. The investigator will absorb other costs associated with the study using discretionary funds. The breakdown is as follows:

A. Routine healthcare costs include

1. On treatment and post treatment:
- Comprehensive metabolic panel
    - Complete blood count with differential
    - HCV RNA monitoring.
2. Routine HCC monitoring if cirrhotic

B. Study related costs include

1. All screening laboratory tests
2. Screening ECG
3. Fibroscan duringscreening
4. On and post treatment urine protein, urine microalbumin, urine creatinine, urine B2 microglobulin
5. On and post treatment serum cystatin C level
6. On treatment ECG monitoring

Monitoring and Quality Assurance

Six months into the study, an independent panel made up of non-investigators will review all data available to that point to ensure appropriate monitoring. These will include personnel from the Division of Hepatology, Infectious Diseases and Nephrology.

Dr. Chung and Dr. Sise will assess the conduct of the study and review all CRFs, source documents, and regulatory documents every six months. They will monitor HCV RNA data, kidney function data, and tolerability of ledipasvir-sofosbuvir therapy.

Dr. Chung and Dr. Sise will ensure that the study is conducted according to the IRB approved protocol and that all regulations and requirements of the IRB are followed.

8. References

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Appendices

Appendix 1: Study Schedule of Events (12 week treatment)

	Screening		On treatment assessments					Post Treatment Assessments			
	Screening Visit 1	**Screening Visit 2**	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**PT + 4**	**PT+12**	**PT+24**	**PT+40 (1 year follow-up)**
Clinical Assessments			FASTING			FASTING			FASTING		FASTING
Informed consent	x										
Determine Eligilibty	x										
Medical History	x										
Physical Exam	x		x				x				
Height	x										
Weight	x		x	x	x	x	x	x			x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x
Fibroscan[1]	x										
12-Lead EKG	x		x	x			x				
Imaging for HCC (if needed)	x										
AE's	x		x	x	x	x	x	x			
Concomitant Medications	x		x	x	x	x	x	x	x	x	x
Study Drug Dispensing			x		x	x					
Quality of Life Questionnaires			x		x	x	x	x	x	x	x
Laboratory Assessments											
Hematology (with differential)	x		**x**	x	**x**	x	**x**	**x**	**x**	x	x
Complete Metabolic Panel	x		**x**	x	**x**	x	**x**	**x**	**x**	x	x
Coagulation (PT/INR, PTT)	x		x				x				x
Cystatin C	x		x	x	x	x	x	x	x	x	x
HCV RNA	x		**x**		**x**		**x**	**x**	**x**	x	
HCV Genotyping[2]	x										
HIV Ab[3]	x										
Urine Pregnancy[4]	x		x		x	x	x	x			
HbA1c			x						X		X

	Screening		On treatment assessments					Post Treatment Assessments			
	Screening Visit 1	**Screening Visit 2**	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**PT + 4**	**PT+12**	**PT+24**	**PT+40 (1 year follow-up)**
Clinical Assessments			FASTING			FASTING			FASTING		FASTING
Plasma Glucose			x			x			X		X
Cryocrit			x			X			X		X
Rheumatoid Factor			x			X			X		X
Complements C3, C4			x			X			X		X
Fasting Lipid panel			x						X		X
Fasting Serum Insulin			x			X			X		X
CRP			x			X			X		X
Urinalysis	x		x	x	x	x	x	x	x	x	x
Urine Albumin (random)	x	x	x	x	x	x	x	x	x	x	x
Urine B2 microglobin			x	x	x	x	x	x	x	x	x
Urine Creatinine	x	x	x	x	x	x	x	x	x	x	x
Total protein/creatinine ratio (random)	x	x	x	x	x	x	x	x	x	x	x
HBV Surface antigen[5]	X										
Archive Plasma (10ml heparin plasma)			x	X	X	X	x	x	X	x	X
Archive Urine Sample (10ml)	x		x	x	x	x	x	x	x	x	x

1. Fibroscan only if no results from biopsy or prior fibroscan available within 12 months prior to screening
2. HCV genotype only if no results available within 24 months prior to screening
3. HIV Ab only if no results available within 6 months prior to screening
4. Urine pregnancy testing only in WOCBP
5. HBV surface antigen only if no result available within 6 months prior to screening

Appendix 2: Study Schedule of Events (24 week treatment)

	Screening		On treatment assessments						Post Treatment Assessments			
	Screening Visit 1	**Screening Visit 2**	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	Week 24	**PT+4**	**PT+12**	**PT+24**	**PT+40 (1 year follow-up)**
Clinical Assessments			FASTING			FASTING				FASTING		FASTING
Informed consent	x											
Determine Eligilibty	x											
Medical History	x											
Physical Exam	x		x					x				
Height	x											
Weight	x		x	x	x	x	x	x	x			x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x
Fibroscan[1]	x											
12-Lead EKG	x		x	x				x				
Imaging for HCC (if needed)	x											
AE's	x		x	x	x	x	x	x	x			
Concomitant Medications	x		x	x	x	x	x	x	x	x	x	x
Study Drug Dispensing			x		x	x	3 X					
Quality of Life Questionnaires			x		x	x	x	x	x	x	x	x
Laboratory Assessments												
Hematology (with differential)	x		**x**	x	**x**	x	**x**	**x**	**x**	**x**	x	x
Complete Metabolic Panel	x		**x**	x	**x**	x	**x**	**x**	**x**	**x**	x	x
Coagulation (PT/INR, PTT)	x		x				x	x				x
Cystatin C	x		x	x	x	x	x	x	x	x	x	x
HCV RNA	x		**x**		**x**		**x**	**x**	**x**	**x**	x	
HCV Genotyping[2]	x											
HIV Ab[3]	x											
Urine Pregnancy[4]	x		x		x	x	x	x	x			
HbA1c			x							X		X

	Screening		On treatment assessments						Post Treatment Assessments			
	Screening Visit 1	**Screening Visit 2**	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**PT + 4**	**PT+12**	**PT+24**	**PT+40 (1 year follow-up)**
Clinical Assessments			FASTING			FASTING				FASTING		FASTING
Plasma Glucose			x			x				X		X
Cryocrit			x			X				X		X
Rheumatoid Factor			x			X				X		X
Complements C3, C4			x			X				X		X
Fasting Lipid panel			x							X		X
Fasting Serum Insulin			x			X				X		X
CRP			x			X				X		X
Urinalysis	x		x	x	x	x	x	x	x	x	x	x
Urine Albumin (random)	x	x	x	x	x	x	x	x	x	x	x	x
Urine B2 microglobin			x	x	x	x	x	x	x	x	x	x
Urine Creatinine	x	x	x	x	x	x	x	x	x	x	x	x
Total protein/creatinine ratio (random)	x	x	x	x	x	x	x	x	x	x	x	x
HBV surface antigen[5]	X											
Archive Plasma (10ml heparin plasma)			x	X	X	X	x	x	x	X	x	X
Archive Urine Sample (10ml)	x		x	x	x	x	x	x	x	x	x	x

1. Fibroscan only if no results from biopsy or prior fibroscan available within 12 months prior to screening
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