Investigator Initiated Studies Program Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - Protocol Identification

Study Title:	A prospective multicenter observational study for characterization of renal function G1b CHC patients with CKD-3 treated with grazoprevir plus elbasvir: New monitoring system of *chronic kidney disease* stage using by serum endostatin level
Document Date:	**September 20, 2018**
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1.1 List the objectives. Primary Endpoints: No worsening of renal function of serum endostatin level at 12 weeks after the treatment Secondary Endpoints: 1. Improvement of serum creatinine level at 12 weeks after the treatment 2. Sustained virological response-12 (SVR12) (negative for serum HCV RNA at 12 weeks after the completion of administration) 3. Virological responses at time points other than the primary time point 4. Effect on decrease of serum alanine aminotransferase (ALT) levels (normalization of serum ALT levels [<30 U/L] at 12 weeks after the completion of administration) 5. Completion/discontinuation of therapy, and incidence of adverse events 6. Relationship between SVR12 and drug resistance mutations in NS3/4A and NS5A regions of HCV genome 2.1.2 List the clinical hypotheses. Hypothesis-1: The grazoprevir plus elbasvir treatment might cause an improvement of renal dysfunction (serum endostatin level) of patients with reduced kidney function. Hypothesis-2: The grazoprevir plus elbasvir treatment might be tolerable and show high virological outcomes even for the patients with reduced kidney function.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Our Kyushu University Liver Disease Study (KULDS) Group has reported results on a cohort study of over 1,200 chronic hepatitis C (CHC) patients treated with a dual therapy of pegylated interferon alpha (PEG-IFNα) plus ribavirin (RBV) [1-11] and that of over 850 CHC patients treated with a telaprevir (TVR)- or simeprevir (SMV)-based triple therapy with PEG-IFNα plus RBV [12-29]. Although sustained virological response (SVR) rate has dramatically been improved by using direct-acting antiviral agent (DAA) such as TVR or SMV, treatment discontinuation due to adverse effects has been observed at high rate in elderly patients. In Japan, patients with CHC are getting older year by year. In fact, over 55% of patients receiving the first oral IFN-free DAA dual therapy of asunaprevir (ASV) and daclatasvir (DCV) were aged 70 or over in our cohort study [Ogawa E, et al. Hepatol Res., 2016]. Moreover, they were frequently suffering from *chronic kidney disease (CKD)* due to hypertension, diabetes mellitus, acute kidney injury by medications, and/or aging. Among our 400 patients treated with ASV/DCV, approximately 25% patients were

	suffering from moderate CKD (estimated glomerular filtration rate (eGFR): 30-59 mL/min/1.73 m^2) [Furusyo N, et al. EASL 2016, SAT-225, in Barcelona]. Thus, it is very important whether new regimens for HCV infection are safely used for patients with renal dysfunction. The regimen using grazoprevir plus elbasvir treatment is promising in Japan, because it may safely be used for the elderly patients with renal dysfunction. Indeed, grazoprevir and elbasvir are metabolized in the liver and do not require dose-adjustment for patients with renal dysfunction [Roth D, et al. EASL 2015]. However, no data related to efficacy and safety of the grazoprevir plus elbasvir treatment for Japanese elderly patients (age 76 or older) with renal dysfunction (eGFR<60 mL/min/1.73m^2) have been reported. Therefore, physicians are at a loss whether or not to treat the patients with renal dysfunction due to no evidence. Higher serum endostatin level is associated with lower GFR and higher albuminuria and independently predicts incident CKD in elderly individuals [30] [Ruge T, American Journal of Nephrology, 2014]. No data was found on improvement of serum endostatin level of chronic hepatitis C patients with renal dysfunction after sustained HCV viremia clearance by antiviral treatment. The aim of this study is to investigate the improvement of serum endostatin level of Japanese patients with CKD stage 3 after grazoprevir (NS3/4A protease inhibitor) plus elbasvir (NS5A replication complex inhibitor) treatment by a prospective, multicenter cohort study. Furthermore, we evaluate efficacy and safety of the treatment in the same patients and address the data gap described above. (See attachment on References 1-30)
2.3 Study Design	A prospective multicenter observational study Target Patients: Japanese patients with CKD stage 3 Target patient number: 80 This study is performed by the Kyushu University Liver Disease Study (KULDS) Group. The members are: Kyushu General Internal Medicine Center, Haradoi Hospital (Jun Hayashi, MD.) Kajiwara Clinic (Eiji Kajiwara, MD.) Department of Gastroenterology, Kyushu Medical Center (Makoto Nakamuta, MD.) Center for Liver Disease, Shin-Kokura Hospital (Hideyuki Nomura, MD.) Center for Liver Disease, Kokura Medical Center (Takeaki Satoh, MD.) Department of Hepatology, Hamanomachi Hospital (Kazuhiro Takahashi, MD.)

	Department of Internal Medicine, Kitakyushu Municipal Medical Center (Akira Kawano, MD.) Department of Internal Medicine, Fukuoka City Hospital (Toshimasa Koyanagi, MD.) Department of Internal Medicine, Chihaya Hospital (Kazufumi Dohmen, MD.) Liver Unit, Department of Internal Medicine, Kyushu Central Hospital (Koichi Azuma, MD.) Department of Medicine and Biosystemic Science, Kyushu University Hospital (Shinji Shimoda, MD.) Department of Medicine and Bioregulatory Science, Kyushu University Hospital (Masaki Kato, MD.)
2.4 Study Flowchart	Observation and Test Parameters and Methods The following items will be conducted. Items 7) Serum endostatin level is a main study-specific parameter and require a blood sample volume of 30 mL for each measurement. Items 1) to 6) are performed routinely in clinical settings. [Patient characteristics] gender, age, height, liver histology, prior treatments, allergic history, medical history, and any complications [Hematological parameters] 1) Routine blood test (white blood cell count, neutrophil count, platelet count, hemoglobin level) 2) Coagulation (PT-INR) 3) Biochemistry (LDH, BUN, total bilirubin, direct bilirubin, total protein, albumin, creatinine, Na, K, Cl, amylase, and lipase) 4) Liver function tests (AST, ALT, γ-GTP, ALP) 5) Lipid metabolism (TC, HDL-C, LDL-C, TG) 6) Fibrosis markers (hyaluronic acid, type IV collagen, M2BP, and AFP) 7) Endostatin level 8) HCV genotype 9) HCV gene mutation test 10) HCV RNA level (PCR assay: both TaqMan HCV test and AccuGene m-HCV) 11) IL28B SNPs 12) Liver biopsy/FibroScan

Timing / Items	Baseline	On treatment						Follow up		
		Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 4	Week 8	Week 12

Whole blood test*	x	x	x	x	x	x	x	x	x	x	
Coagulation	x										
Biochemistry	x	x	x		x		x	x	x	x	
AST/AST, γ-GTP, ALP	x	x	x		x		x	x	x	x	
Lipid metabolism (TC, HDL-C, LDL-C, TG)	x						x			x	
Fibrosis markers (AFP, hyaluronic acid, type IV collagen, M2BP)	x		x		x		x			x	
Endostatin level	x	x	x		x		x	x		x	
HCV Genotype	x										
HCV gene mutation test	x										
HCV RNA level (PCR assay: TaqMan+AccuGene)	x		x		x		x	x	x	x	
IL28B SNPs	x										
Liver biopsy or FibroScan	x										

*: Whole blood test includes white blood cell count, neutrophil count, platelet count, and hemoglobin level

2.5 Study Procedures

Patients who have received sufficient explanation for participation in the study, and who have submitted a written form of informed consent by their own freewill after thorough understanding.

Inclusion Criteria:

1. Subjects aged 20 years or older.
2. Patients positive for HCV RNA for over 6 months and infected with genotype 1b chronic hepatitis C, including compensated cirrhosis.
3. Patients without co-infection of hepatitis B virus.
4. Patients without co-infection of human immunodeficiency virus
5. Patients with moderate chronic kidney disease (CKD stage 3) (eGFR: 30-59 mL/min/1.73m^2). A diagnosis of CKD is only confirmed if repeated eGFR tests for at least 90 days.

Exclusion Criteria:

1. Patients with decompensated cirrhosis (Child Pugh B and C)
2. Patients with albumin <3.0 g/dL and platelets <75,000 /μL
3. Patients with autoimmune hepatitis
4. Constant heavy alcohol drinkers (converted to ethanol ≥60 g/day) 5. Patients who have a history of hypersensitivity to grazoprevir and elbasvir

	6. Patients who are pregnant females, or females who may become pregnant, or females who are breastfeeding 7. Patients with heart disease that is hard to control (e.g., very recent cardiac infarction, severe heart failure, unstable arrhythmia) 8. Patients who are under medication with drugs listed as contraindication in a package insert of grazoprevir plus elbasvir treatment 9. Patients judged (by the physician in charge of research) to be inappropriate as subjects for the study for any other reasons. After informed consent is obtained, administration is to be conducted according to the following dose/injection route: An oral dose of 100 mg/day of grazoprevir as well as an oral dose of 50 mg/day of elbasvir for 12 weeks. During the study, therapy shall be conducted safely after confirmation of the presence or absence of adverse events, results of serologic tests, and the blood cell count. Each patient is followed up every 2 to 4 weeks until 12 weeks after completion of therapy. Discontinuation criteria: Serologic tests, including liver function and blood cell counts (white blood cell count, neutrophil count, platelet count, hemoglobin level), should be conducted during therapy, more than twice a week within 1 week after initial administration and regularly every week thereafter to consider the necessity of discontinuation. The patient may be discontinued from the study at the discretion of the investigator according to the status of the patient if adverse events develop.
2.6 Study Duration	From the time of approval of the IRB to 31 March, 2020
2.7 Statistical Analysis and Sample Size Justification	State who will be responsible for analyzing the study data (Investigator, contract CRO, etc.). When appropriate state how the blind will be maintained during the study, as appropriate, and when the data will be un-blinded. For the purpose of the final analysis, the official clinical database will not be un-blinded until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data has been declared complete. Variables/Time Points of Interest: All variables (primary and secondary) that are listed in the study hypotheses, and the time points at which they will be analyzed, need to be described in detail. Efficacy variables discussed in this section should have been included as part of an objective or hypothesis section. These variables and the time points at which they are to be analyzed should be consistent with the primary and secondary hypotheses, i.e., primary variables and time points should relate to the primary hypotheses. Statistical Method: Statistical analyses will be conducted using SPSS Statistics version 22.0 (IBM SPSS Inc., Chicago, IL, USA). A P value less than 0.05 will be regarded as statistically significant in all analyses. Variables with P value <0.10 in univariate analysis will be evaluated using multivariate logistic regression to identify

	variables significantly associated with SVR12. The results will be expressed as odds ratios and their 95% confidence interval (CI). Each endpoint such as SVR12, Adverse event frequency, tolerability, ALT normalization will be summarized with mean and 95% CI. Drug concentration will be summarized with trough concentration and 95% CI. Power/Sample Size: Although there is no report (or literature) on the improvement of serum endostatin levels after eradication of HCV, we hypothesize that endostatin levels would be improved in 50% of patients with SVR and 5% of patients without SVR. According to Japanese Phase 3 trial, the SVR rate of this regimen is 90%. We estimate the proportion of SVR would be 97%. In this case, 76 patients are necessary and sufficient to detect differences between two groups with 2-side alpha=5% and power=80%. Since the dropout rate of patients is approximately 5%, the estimated sample size should be 80. We set the sample size based on the feasibility of this exploratory study.
2.8 Specific Drug Supply Requirements	None (Obtain from market by PI)
2.9 Adverse Experience Reporting	The Investigator-Sponsor will report Serious Adverse Experiences to Merck Global Safety and any local regulatory agency (as applicable) as per the study agreement. Adverse Event An adverse event means any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with any use of the Merck product whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the product, is also an adverse experience. Serious Adverse Event A serious adverse event (SAE) is any adverse event occurring at any dose that: · Results in death · Is life threatening (places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred) · Results in a persistent or significant disability/incapacity · Results in or prolongs an existing inpatient hospitalization · Is a congenital anomaly/birth defect Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the

	subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not require hospitalization, or development of drug dependency or drug abuse. · Is an overdose (whether accidental or intentional) · Cancer (that is not the condition under the study)* *If disease progression is noted during a protocol-specified reevaluation of the status of a patient's cancer and the progression is manifested solely by results of tumor markers and/or radiologic imaging, that occurrence of progressive disease will NOT be recorded as an adverse experience. All Serious Adverse Event, regardless of causal relationship to the investigational product, must be forwarded via Fax to MSD KK Pharmacovigilance group via fax (81-3-6238-9191) within 2 working days of the investigator becoming aware of the event Non-Serious Adverse Event All Non-Serious Adverse Event, regardless of causal relationship to the investigational product, must be forwarded via Fax to MSD KK Pharmacovigilance group via fax (81-3-6238-9191) annually and the due date for the reporting will be defined in the CTRA.
2.10 Itemized Study Budget	A preliminary study budget must be provided with the initial proposal submitted to give guidance to the MISP Review Committee as to the expected study costs. A refined itemized budget detailing the costs associated with the study should be provided with the final protocol or included in the study agreement as Exhibit B.
2.11 References	References related to this study [1] Furusyo N, Kajiwara E, Takahashi K, Nomura H, Tanabe Y, Masumoto A, Maruyama T, Nakamuta M, Enjoji M, Azuma K, Shimono J, Sakai H, Shimoda S, Hayashi J: Association between the treatment length and cumulative dose of pegylated interferon alpha-2b plus ribavirin and their effectiveness as a combination treatment for Japanese chronic hepatitis C patients: A project of the Kyushu University Liver Disease Study Group. Journal of Gastroenterology and Hepatology 23 (7): 1094-1104, 2008. [2] Ogawa E, Furusyo N, Toyoda K, Takeoka H, Maeda S, Hayashi J: The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. Antiviral Research 83 (2): 127-134, 2009. [3] Ogawa E, Furusyo N, Toyoda K, Taniai H, Otaguro S, Kainuma M, Murata M, Sawayama Y, Hayashi J: Excellent superiority and specificity of COBAS TaqMan HCV

assay in an early viral kinetic change during pegylated interferon-alpha 2b plus ribavirin treatment. BMC Gastroenterology 10: 38, 2010.

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of chronic hepatitis C patients receiving telaprevir-based triple therapy: A comparison of two real-time PCR assays. Antiviral Research 99 (2): 119-124, 2013.

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	with simeprevir for chronic hepatitis C genotype 1b patients with prior telaprevir failure. Journal of Viral Hepatitis 22 (12): 992-1001, 2015. [24] Ogawa E, Furusyo N, Dohmen K, Kajiwara E, Kawano A, Nomura H, Takahashi K, Satoh T, Azuma K, Nakamuta M, Koyanagi T, Kotoh K, Shimoda S, Hayashi J; The Kyushu University Liver Disease Study (KULDS) Group: Comparative effectiveness and safety study of triple therapy with simeprevir or telaprevir for non-cirrhotic patients with chronic hepatitis C virus genotype 1b infection. Journal of Gastroenterology and Hepatology 30 (12): 1759-1767, 2015. [25] Hiramine S, Sugiyama M, Furusyo N, Uto H, Ido A, Tsubouchi H, Watanabe H, Ueno Y, Korenaga M, Murata K, Masaki N, Hayashi J, Thomas DL, Mizokami M. A thymine-adenine dinucleotide repeat polymorphism near IL28B is associated with spontaneous clearance of hepatitis C virus. Journal of Gastroenterology 50 (10): 1069-1077, 2015. [26] Hiramine S, Furusyo N, Ogawa E, Nakamuta M, Kajiwara E, Nomura H, Dohmen K, Takahashi K, Satoh T, Azuma K, Kawano A, Koyanagi T, Kotoh K, Shimoda S, Hayashi J. Importance of virological response in the early stage of telaprevir-based triple therapy World Journal of Hepatology 7 (26): 2688-2695, 2015. [27] Ura K, Furusyo N, Ogawa E, Hayashi T, Mukae H, Shimizu M, Toyoda K, Murata M, Hayashi J. Serum WFA+-M2BP is a non-invasive liver fibrosis marker that can predict the efficacy of direct acting antiviral-based triple therapy for chronic hepatitis C. Alimentary Pharmacology & Therapeutics 43 (1): 114-124, 2016. [28] Ogawa E, Furusyo N, Murata M, Hayashi T, Shimizu M, Mukae H, Toyoda K, Hotta T, Uchiumi T, Hayashi J. Impact of HCV kinetics on treatment outcome differs by the type of real-time HCV assay in NS3/4A protease inhibitor-based triple therapy. Antiviral Research 126: 35-42, 2016. [29] Hayashi T, Ogawa E, Furusyo N, Murata M, Hayashi J. Influence of insulin resistance on the development of hepatocellular carcinoma after antiviral treatment for non-cirrhotic patients with chronic hepatitis C. Infectious Agents and Cancer 11: 9, 2016. [30] Shimizu M, Furusyo N, Tanaka Y, Kato Y, Mitsumoto-Kaseida F, Takayama K, Ura K, Hiramine S, Hayashi T, Ikezaki H, Ihara T, Mukae H, Ogawa E, Toyoda K, Kainuma M, Murata M, Hayashi J. The relation of postprandial plasma glucose and serum endostatin to the urinary albumin excretion of residents with pre-diabetes: Results from the Kyushu and Okinawa Population Study (KOPS). International Urology and Nephrology 2016 (in press).
2.12 Publication Plan	Hepatology, Journal of Hepatology, Journal of Gastroenterology (72 weeks after the start of study) AASLD, EASL, APASL (2017-2018)
2.13 Curriculum Vitae	Attached
2.14 Protocol Submission for Investigator-Initiated Studies	Non U.S. protocols should be submitted to the MSD office by the investigators.