Section 1. General Information

Protocol Title: Safety, Efficacy, and Changes in Traditional and Novel Biomarkers of Kidney Function in Patients with Hepatitis C and Chronic Kidney Disease treated with Viekira Pak or Mavyret

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Section 2. Background information

Rationale and Background Information:

Chronic kidney disease (CKD) is common in Hepatitis C virus (HCV) infected individuals. Between 55-85% of HCV infected patients with cirrhosis have some form of glomerular disease on kidney biopsy.[1, 2] It is well established that HCV increases the risk of progressive CKD; patients with HCV are 34-68% more likely to develop end-stage-renal disease (ESRD) than non-infected patients.[3-5] Despite the advances in all oral therapies for HCV infection over the last 2 years, there is still tremendous need for data to guide how to treat HCV infected patients with advanced kidney disease. The Abbvie Viekira Pak was approved by the FDA on December 19th, 2014 to treat genotype 1 infection and Mavyret, a pangenotypic combination regimen of glecaprevir and pibrentasvir, was approved in August 2017 with no dose adjustments necessary for mild to severe renal impairment. However no published series have looked explicitly at this population to determine the effect on historical and novel biomarkers of CKD and renal inflammation. Historically, achieving sustained virologic response (SVR), with pegylated interferon and ribavirin therapy has been shown to improve kidney function and decrease the rate of progression of CKD.[6-10] The mechanism behind the link between HCV infection and CKD progression is not fully understood, but likely involves promotion of insulin resistance, chronic inflammation, and the potential for immune complex deposition in the glomerulus of the kidney. The new era of DAA therapy allows for the opportunity to better characterize the mechanisms that promote CKD by studying the reversibility of markers of kidney disease and chronic inflammation with eradication of HCV. We hypothesize that patients with advanced CKD will demonstrate improvement in proteinuria and eGFR after viral eradication with either Viekira Pak or Mavyret per current standard of care guidelines found at HCVguidelines.org.

The new era of HCV therapy allows us to test the reversibility of the association between HCV infection and CKD. Our data in patients with cryoglobulinemia shows that patients with active glomerulonephritis treated with novel direct antiviral agents (DAA) had a 70% reduction in proteinuria and a 12.6mL/min improvement in eGFR by SVR12 [11]. Reduction in proteinuria is an important component of the definition of clinical remission in treatment of glomerular diseases and a widely accepted surrogate for CKD progression.[12, 13]

Cystatin-C based eGFR estimates have been shown to outperform creatinine-based estimates in terms of predicting cardiovascular events and mortality; this is likely related to the fact that in addition to measuring kidney function, serum cystatin-C also reflects the inflammatory milieu.[14-18] Urine studies, such as albuminuria and proteinuria are heavily relied on by nephrologists to predict which patients are going to develop progressive CKD. Albuminuria is common in HCV infection, however it is typically not screened for, nor routinely monitored in patients with HCV infection undergoing therapy.[19, 20] Citations for the rational for measuring novel CKD biomarkers are listed below.

It is well established that HCV infection is a risk factor for CKD progression. We propose that this data could serve as the basis to support further study into the role of HCV eradication to slow CKD progression in patients with HCV. If HCV is a reversible risk factor for progressive CKD, then the implications of this finding will be far-reaching. Slowing progression of kidney disease is a critical goal in the field of nephrology, as the increasing incidence and prevalence of advanced CKD and ESRD places significantly increased health burden on patients and tremendous costs on our health-care system.

Section 3. Core Protocol

3.1 Study Objectives and Purpose:

The objective of this study is to evaluate the effect of HCV eradication with Viekira Pak or Mavyret for adults with CKD with an estimated glomerular filtration rate (eGFR) 15-60 ml/min that are infected with hepatitis C virus (HCV) genotype 1-6, to determine the effect of treatment on traditional and novel markers of kidney function and cardiovascular disease risk in patients with advanced CKD. During the course of this prospective, single arm treatment trial, we will measure currently accepted markers of kidney function and novel biomarkers of CKD progression to determine if they improve with eradication of HCV.

Aim 1. Determine the effect of HCV eradication with Viekira Pak or Mavyret on traditional and novel makers of CKD progression in 10 patients with CKD (eGFR 15 - 60) who are pre-dialysis who undergo therapy of HCV infection. Measure novel biomarkers of incident and progressive CKD and liver disease to determine if eradication of HCV infection changes measures of chronic inflammation associated with progressive end-organ disease. Repeated measures will be taken at baseline and regular study intervals.

Aim 1. Determine the safety, tolerability, efficacy, and effect on quality of life of Viekira Pak or Mavyret in 10 patients with CKD (eGFR 15 – 60mL/min) who are pre-dialysis. Patient visits at baseline, week 2, 4, 8, 12, and SVR 12 to assess safety, adverse reactions, and perform measurements for Aim 1.

We hypothesize that that traditional and novel markers of CKD will improve with HCV eradiation and that Viekira Pak or Mavyret will be safe and effective and lead to improvement in quality of life in patients with advanced CKD.

3.2. Study Design

This will be a single arm, open-label experimental trial conducted at Massachusetts General Hospital. There will be no control or placebo arm. Massachusetts General Hospital will be the single study center

Ten patients with CKD (estimated glomerular filtration rate (eGFR) between 15mL/min and 60mL/min. We expect 5 patients with have stage 3b or 4 CKD (GFR 15-45) and 5 patients will have stage 3A CKD (eGFR 45-60). Due to the fact that the vast majority of patients with eGFR < 20mL/min are referred for kidney transplant evaluation and strongly encouraged to undergo transplantation from HCV infected donors prior to receiving DAA therapy in order to dramatically shorten transplant waitlist time, this pool of patients is largely left untreated at the request of our transplant center. This significantly limits our ability to recruit patients whose GFR is approaching 20mL/min. Thus, in order to complete this study in a timely fashion, we propose including patient with eGFR up to 60mL/min to improve our ability to rapidly recruit patients into this study. Futhermore, stage 3A and 3B CKD are the stages where interventions such as eradicating HCV are most likely to be able to slow eGFR decline this is an important population to study.

If eligible, they will undergo treatment. The expected duration of study participation is 58 weeks, this time period includes a 30 day screening period, followed by 12 weeks of therapy with Viekira Pak or Mavyret and a total of one year of follow-up. A study timeline is provided showing the sequence and duration of all study periods.

Figure 1. Study Timeline

365
[1yr f/u]

3.3 Inclusion Criteria

1. The subject has signed the written informed consent
2. Male or female ≥ 18 year of age
3. HCV genotype 1-6 with ribonucleic acid (HCV RNA) greater than 1000IU/mL, determined by HCV RNA polymerase chain reaction Roche COBAS TaqMan quantitative assay
4. 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 that they take Viekira Pak or Mavyret and 90 days after finishing Mavyret. If their regimen includes ribavirin, they must agree to this for 6 months 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

5. Male subjects must agree to consistently and correctly use a condom during heterosexual intercourse and avoid sperm donation for the duration that they take Viekira Pak or Mavyret and 90 days after finishing Mavyret. If their regimen includes ribavirin, they must agree to this for 7 months after the last dose of if ribavirin. 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 7 months after last study drug date. Hormone-containing contraceptive options for partners include implants of levonorgestrel, injectable progesterone, oral contraceptives, contraceptive vaginal ring, or transdermal contraceptive patch
6. Estimated glomerular filtration rate 15-60mL/min/1.73m^2 as estimated by CKD-Epi equation [22]
7. Liver imaging to exclude HCC is required within 6 months in any patient with cirrhosis

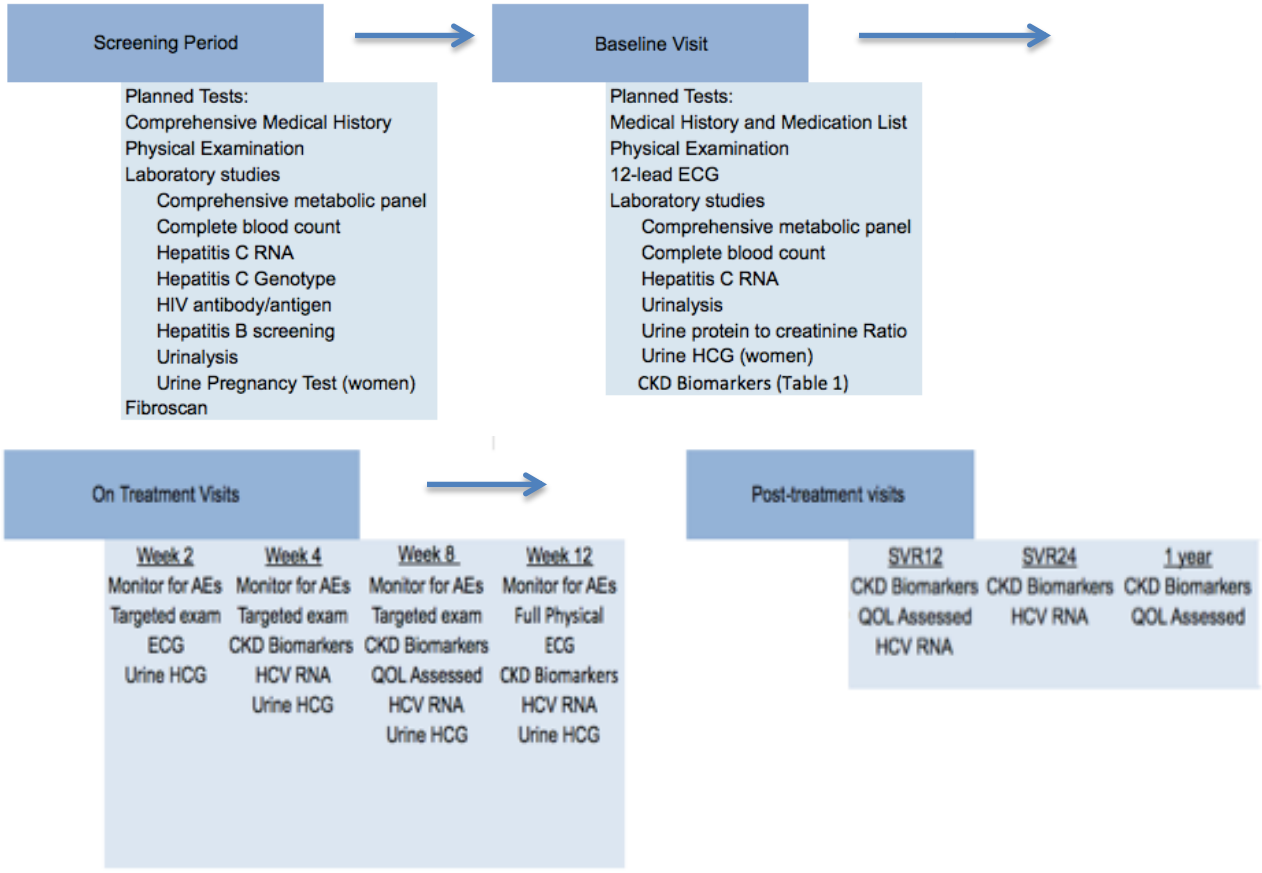
3.4 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will 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. History of decompensated cirrhosis, Child-Pugh Class B/C cirrhosis
3. Pregnant or lactating female
4. Uncontrolled depression or psychiatric disease interfering with the ability to comply with the study procedures or complete the study
5. 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, 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
6. Experiencing life-threatening cryoglobulinemic vasculitis requiring initiation of rituximab, steroids or plasmapheresis.
7. Concomitant use of red yeast rice, St. John's Wort, Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin, efavirenz, atorvastatin, lovastatin, simvastatin during the study period. Use of pravastatin allowed if dose reduced by 50% and rosuvastatin allowed up to a dose of 10mg daily if taking Mavyret. Concomitant use of alfuzosin, carbamazepine, ergot derivatives, ethinyl estradiol containing products, efavirenz, gemfibrozil, lovastatin, midazolam, phenobarbital, phenytoin, pimozide, rifampin, sildenafil, simvastatin, St. John's wort, triazolam if taking Viekira Pak.
8. Uncontrolled cardiovascular or pulmonary disease
9. Known hypersensitivity to ribavirin, dasabuvir, ombitasvir, paritaprevir or ritonavir
10. Experiencing symptoms attributed to uremia: nausea, vomiting, asterixis, and pericardial effusion without another cause.
11. Treating nephrologist anticipates the need to begin renal replacement therapy in the next 6 months
12. Inadequate hematologic parameters defined as follows platelets < 50 x 10^9/L or hemoglobin < 9 g/dL despite use of erythropoietin stimulating agent
13. Previously treatment experienced with a NS5A inhibitor class medication or previously treated with Mavyret
14. Patients with genotype 3 infection with any direct-acting antiviral exposure will be excluded.
15. Kidney transplant recipient

3.5. Study Flowchart

Figure 2. Study Flowchart



3.6 Study Procedures

This will be a single-arm unblinded trial evaluating the safety and efficicacy and effects of HCV eradication with Vikiera Pak or Mavyret on kidney function and markers of CKD progression.

Initial Screening Period
Patients will be asked to perform two screening visits. At the first visit they will be screened for eligibility according to the above inclusion and exclusion criteria. They will also have screening blood and urine tests performed. Patients will undergo Fibroscan to determine the degree of cirrhosis unless they have a prior biopsy documenting cirrhosis. At this visit they will undergo informed consent and participant and investigators will each receive a copy of the signed consent form. The primary purpose of the second screening visit is to establish a stable baseline level of renal function including cystatin C and creatinine based estimated GFR estimate and proteinuria level.

Baseline Visit
At the baseline visit, patients will undergo full medical history and physical examination, ECG monitoring, quality of life assessment with SF36 and FACIT-F (a fatigue scale). Patients will undergo venous sampling for routine bloodwork and sampling of blood and urine for study assays (**Table 1a and 1b**). Patients will receive the first four weeks of study drug at the baseline visit.

Table 1a. Traditional Markers of CKD Progression
Measured at Baseline, Week 4, Week 8, Week 12 or 16 (if needed), SVR4, SVR12, SVR24 and 1 year

Serum creatinine (mg/dL)
Serum cystatin C (mg/L)
Urine total protein (mg/dl) / urine creatinine (mg/dl) ratio
Urine albumin (mg/dl) / urine creatinine (mg/dl) ratio
White blood cell differential – monocyte count linked to CKD progression and atherosclerosis[23]

Table 1b. Novel Markers of CKD Progression
Measured at Baseline, Week 8, SVR12, and 1 year follow-up

Serum FGF-23– validated marker of incident and progressive CKD[24]
Serum CRP – marker of incident and progressive renal failure[25, 26]
Serum and Urine IL-6 - marker of incident and progressive renal failure[25, 26]
TNF-alpha receptor - marker of incident renal failure[26]
Soluble CD163 – liver fibrosis, marker of macrophage activity, implicated in mechanism of immune complex kidney disease[27]
Urine neutrophil gelatinase associated lipocalin (NGAL) – correlates with more advanced fibrosis on kidney biopsy[28] and with incident CKD[29] and cardiovascular mortality in CKD[30].

Dosing regimen
Patients will be prescribed DAA therapy (Viekira Pak or Mavyret) based on current standard of care. We will submit the prescription for approval by their insurance company. If insurance approval is denied, or if the patient is uninsured, the treatment course will be provided by Abbvie.
On label use of the Viekira or Mavyret regimen will follow recommendations provided by the AASLD and IDSA, (HCVguidelines.org, accessed 10/11/17).

Patient receiving Mavyret:
1. Genotype 1-6 noncirrhotic, treatment naïve patients will receive 8 weeks of Mavyret

2. Genotype 1-6 with cirrhosis, treatment naïve patients will receive 12 weeks of Mavyret

3. Genotype 1, 2, 4, 5, 6 patients treatment experienced with either interferon, ribavirin, sofosbuvir, or a protease inhibitor will receive 12 weeks of Mavyret

4. Genotype 3 patients that are treatment experienced with either interferon and/or ribavirin will receive 16 weeks of Mavyret

Patients receiving Viekira-Pak based regimens:

Genotype 1a - Paritaprevir (150mg)/ritonavir (100mg)/ombitasvir (25mg), once daily, dasabuvir (250mg) twice daily, ribavirin 200mg-400mg daily (based on eGFR) for 12 weeks. Excluded if cirrhotic.
Genotype 1b. Paritaprevir (150mg)/ritonavir (100mg)/ombitasvir (25mg) once daily, dasabuvir (250mg) twice daily for 12 weeks. Ribavirin 200mg daily added if there is a history of cirrhosis. Initial Ribavirin dosing will follow package insert and begin with 200mg daily for patients with <30mL/min/1.73m^2. Dose adjustments for anemia will follow published guidelines.[30]
Genotype 4 – Paritaprevir (150mg)/ritonavir(100mg)/ombitasvir (25mg) once daily and ribavirin 200-400mg (based on eGFR) once daily for 12 weeks.

On-Treatment Follow-up visits – Treatment period will be based on standard of care for all subjects
Patients will undergo a follow-up visit at 2 weeks, 4 weeks, 8 weeks and 12 and 16 weeks if needed on therapy and monitoring for adverse events by the study investigators with history and targeted physical exam and with routine bloodwork will occur at every study visit. Routine 12 lead ECG will be monitored on week 2 and end of treatment. Quality of life measures will be taken at 8 weeks on therapy. Traditional CKD biomarkers (**Table 1a**) will be measured at week 4, 8, and 12. Novel biomarkers (**Table 1b**) will be measured at week 8 on treatment.

Post-Treatment Follow-up Visits
Patients will undergo four post-treatment follow-up visits at SVR4 (4 weeks after treatment ends) SVR12 (12 weeks after treatment ends), SVR24 (24 weeks after treatment ends) and 1 year follow-up (day 365). Kidney function tests and novel biomarker analysis will be assessed at each of these visits. AEs will be recorded at SVR4 and the study investigator will determine if it is treatment-related or not. Quality of life assessments (SF36 and FACIT-F) will be measured at SVR12 and 1 year visit. Traditional CKD biomarkers (**Table 1a**) will be measured at all follow-up visits. Novel biomarkers (**Table 1b**) will be measured at SVR12 and 1 year follow-up.

Withdrawal Criteria
Patients will be monitored carefully for any side effects or adverse events. Serum laboratory results will be monitored at every study visit. Dr. Sise will review results. If indicated, subjects may be asked to visit more frequently for monitoring if any abnormalities are found. If at any time adverse effects are experienced by the subjects, they will have 24-hour access to speak with a member of the study staff, we will immediately provide the appropriate medical and professional intervention. At any time, Dr. Chung and Dr. Sise have the right to withdraw patients due to concurrent illness, adverse events, or treatment failure. These conditions are include: 1) Pregnancy of female subject 2) Efficacy/Virologic Failure (defined below) and 3) Significant adverse event requiring termination of study drugs 4) Dr. Chung and Dr. Sise feel it's in the best interest of the patient to stop study participation for medical safety 5) If the study is stopped by the, IRB or the FDA the patient will be removed from the protocol and followed for safety reasons only. If a subject is withdrawn prior to receiving the first study medication dose then they will be replaced. If a subject is withdrawn from the trial after receiving ≥ 1 dose of study medication then they will not be replaced. Patients who are withdrawn from the trial treatment will still undergo visits at all scheduled follow-up time-points up until 1 year as originally planned.

Virologic Failure Study Withdrawal Criteria
- Confirmed HCV RNA ≥ LLOQ after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 log10 increase from nadir
- HCV RNA ≥ LLOQ through 8 weeks of treatment

Drs Chung and Sise will serve as the data safety monitoring board (DSMB). Once 1/3 of the subjects have been enrolled and again after 2/3 of subjects have enrolled, the Dr Chung and Sise will meet and can stop the study based on the safety of therapy.

Safety will be evaluated by clinical laboratory tests, physical exam, vital signs measurements and by the documentation of AEs. Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days.

Summaries of treatment-emergent adverse events will be provided for the following (1) All AEs (2) All study drug-related AEs (3) All grade 3, 4 AEs (4) All study drug-related grade 3, 4 AEs (5) All AEs leading to permanent discontinuation of the study drug (6) All SAEs (7) All study drug related SAEs. Pertinent laboratory data will be summarized and corresponding change from Baseline/Day 1 will be presented throughout the study period. Graded laboratory abnormalities will be defined using the standard WHO laboratory toxicity grading.

To evaluate the safety and tolerability of each treatment regimen as assessed by review of the accumulated safety data by determining the number of adverse events leading to discontinuation of the regimen. Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drug through the date of last dose of study drug plus 30 days.

Publication Plan

Presentation at Conferences:
Presentation of preliminary results at AASLD 2018
Presentation of renal biomarker results at American Society of Nephrology 11/2019

Manuscript:
Publication in Hepatology or Journal of the American Society of Nephrology - Submission December 2019

3.7 Statistical Analysis and Sample Size Justification

Statistical analysis: Summary statistics of baseline characteristics for all patients will be described. Demographic and baseline characteristics will be summarized using standard descriptive methods and will include age, sex, and self-identified race/ethnicity. Baseline characteristic data will include body mass index, HCV RNA level ($\log_{10}$ IU/mL), genotype HCV infection, and additional comorbidities (cirrhosis, diabetes, hypertension, HIV infection). The number (proportion of subjects) in each genotype stratum and response to prior HCV therapy will be summarized.

With N = 10 patients included we conservatively estimate that at least 9 will achieve SVR. With 10 patients each with 4 measurements of novel and traditional kidney and cardiovascular risk biomarkers over time the anticipated number of measurements will be 40.

Pre-and post eGFR by creatinine, cystatin C will be compared by paired sample t-test (baseline vs. SVR12 measurement). Changes from baseline to all follow-up visits of the levels of all markers in **Table 1** will be assessed using a maximum-likelihood, mixed-effects repeated-measures model (MMRM) with all longitudinal observations included. The model will include terms for baseline and all subsequent visits (on-treatment, short-term and long-term follow-up). Means and 95% confidence intervals will be presented for change in markers from baseline through each follow-up visit. Analyses

will be performed using PROC MIXED with denominator degrees of freedom estimated by the Satterthwaite approximation. Covariance structure will be determined using the lowest Akaike information criterion. P values will be presented for each post-baseline visit as well as for all follow-up visits combined. In order to determine the kinetics of marker reduction, we will determine the average time in weeks until nadir. Outcomes will be checked for normality to meet the assumptions of parametric testing; appropriate transformations or non-parametric tests will be utilized. As an exploratory analysis, we will determine which pathway is the most influential on renal recovery. I will correlate improvements in eGFR and proteinuria with changes in novel biomarkers. I will evaluate the kinetics of improvement in these biomarkers as a recapitulation of the relative contributions of each. We expect an attenuated decline from baseline through each of the follow-up periods.

3.8 Specific Drug Supply Requirements

Detailed information for study shipment is provided in the attached form. The primary investigators will be responsible for proper handling and safe and secure storage. Clinical supplies will only be dispensed in accordance with the protocol. The primary investigators will be responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study.

3.9 Safety Reporting

Safety will be evaluated by clinical laboratory tests, physical exam, vital signs measurements and by the documentation of AEs. Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days.

Summaries of treatment-emergent adverse events will be provided for the following (1) All AEs (2) All study drug-related AEs (3) All grade 3, 4 AEs (4) All study drug-related grade 3, 4 AEs (5) All AEs leading to permanent discontinuation of the study drug (6) All SAEs (7) All study drug related SAEs. Pertinent laboratory data will be summarized and corresponding change from Baseline/Day 1 will be presented throughout the study period. Graded laboratory abnormalities will be defined using the standard WHO laboratory toxicity grading.

The investigators will report all SAEs within 24 hours of learning of the event regardless of the relationship of the even to the AbbVie product. If requested, the Principle Investigator will make pertinent records available to AbbVie promptly. Any submission of the events to the FDA will copy Abbvie. If any subject receiving an AbbVie product has a pregnancy that results in a negative outcome or untoward event during pregnancy or upon delivery.

Non-serious AEs will be collected and reported and reviewed by the study investigators. Any non-serious AE that occurs with unexpected frequency will be reported as an unexpected event and reported to IRB and AbbVie. All AEs will be reviewed within 24 hours by Dr. Sise and Chung.

3.10 References

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