MSK PROTOCOL COVER SHEET

IIT: Phase 2 Study of Colesevelam for Lenalidomide-Associated Diarrhea

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title

Colesevelam for lenalidomide-associated diarrhea

Primary Objective

The primary objective is to evaluate the ability of colesevelam to improve lenalidomide-associated diarrhea in patients with multiple myeloma treated with lenalidomide maintenance.

Patient population

Patients with multiple myeloma, age 18 years or older, treated with maintenance lenalidomide. Patients who experience grade 1 or worse diarrhea on lenalidomide will be treated with colesevelam.

Study design

This is a single arm, phase II trial of colesevelam for lenalidomide-associated diarrhea. Up to 40% of myeloma patients on lenalidomide maintenance experience some degree of diarrhea.[1,2] There is currently no established treatment standard for patients who develop diarrhea during lenalidomide and available anti-diarrheal (i.e. loperamide, opioids) may not give optimal symptom relief. In this trial we will assess whether colesevelam, a bile acid sequestrant, can improve diarrhea associated with lenalidomide maintenance therapy in patients with grade 1 or more diarrhea. The target will be that 30% of patients with lenalidomide-associated diarrhea will have an improvement by at least 1 grade or returns to patients baseline when receiving colesevelam. A total of 25 patients will accrue on the study in a Simon's two-stage minimax design. Patients will initially be started on 1250 mg (2 x 625 mg tablets) and the dose can be increased to maximum of 6 tablets per day based on efficacy and tolerability. Treatment will be continued until drug-related toxicity, worsening of diarrhea, or diarrhea that remains grade 1 or higher at week 2. Each patient will be followed for 12 weeks after colesevelam initiation.

Secondary objectives in the study include assessment of gastrointestinal (GI) symptoms the Patient Reported Outcomes within the Common Terminology Criteria for Adverse Events (PRO-CTCAE), as well as assessment of diet using a dietary questionnaire.

Lenalidomide pharmacokinetics will be assessed in up to 15 patients to assess possible drug interactions between lenalidomide and colesevelam. In these patients, a blood sample will be drawn pre- and 2 hours post the first colesevelam dose (day 1), as well as pre- and 2 hours post colesevelam on day 8 after initiation of colesevelam. Research stool samples will be collected at baseline and after 12 weeks of treatment for microbiota and bile acid studies.

Treatment Plan

Patients will be treated with colesevelam, starting dose 1250 mg (2 x 625 mg tablets) which can be increased to up to 6 tablets per day based on efficacy and tolerability. Response will be evaluated after 1, 2, 4, and 12 weeks after start of colesevelam. Patients will be treated with colesevelam on the study for up to 12 weeks.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective

To evaluate the ability of colesevelam to improve lenalidomide-associated diarrhea in patients with multiple myeloma treated with lenalidomide maintenance. Diarrhea will be evaluated using Common Terminology Criteria for Adverse Events (CTCAE) grading. The primary end-point is improvement of diarrhea by at least 1 grade or returns to patients baseline when receiving colesevelam according to CTCAE 5.0 scale by 4 weeks of treatment with colesevelam.

Secondary objective

- To assess GI symptoms using the Patient Reported Outcomes within the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
- To assess diet before and while on treatment with colesevelam.
- To further describe diarrhea during the study period using the Bristol Stool Form Scale.[3]
- Describe duration of response by week 12 (end of study)

Correlative studies

- To assess lenalidomide pharmacokinetics while on colesevelam
- Collection of research stool samples for GI microbiota and bile acid assessment

3.0 BACKGROUND AND RATIONALE

Multiple Myeloma – Disease Overview

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by hypercalcemia, anemia, renal insufficiency, lytic bone disease, or other myeloma-related events (serum free chain ratio ≥100, >1 focal lesions on PET-CT or magnetic resonance imaging, or >60% clonal plasma cells in the bone marrow). Multiple myeloma accounts for 1% of all cancers and 10-15% of all hematological malignancies. Median age at diagnosis is 69 years. According to data from the Surveillance, Epidemiology, and End Results program, 30,770 new myeloma cases are estimated to be diagnosed in 2018 in the US.

Myeloma is treated with induction therapy where the standard in young and fit patients is a combination of three drugs with different mechanisms of action. The most common three-drug combinations are carfilzomib/lenalidomide/dexamethasone or bortezomib/lenalidomide/dexamethasone. Induction therapy is followed by consolidation therapy which may include high-dose melphalan chemotherapy with autologous stem cell transplantation. Induction and consolidation treatment is in the majority of patients followed by maintenance therapy with lenalidomide.

Lenalidomide and Multiple Myeloma

Lenalidomide (Revlimid®) is an immunomodulatory (IMiD) compound with anti-neoplastic activity that stems from several potential mechanisms of action, including direct induction of apoptosis, inhibition of angiogenesis, and inhibition of pro-survival signals to tumor cells and stimulation of host anti-tumor immunity. Lenalidomide is FDA approved for maintenance in multiple myeloma.[4] According to several clinical trials and a recent meta-analysis, lenalidomide maintenance prolongs progression-free survival and overall survival.[2,5-8]

Lenalidomide-associated diarrhea

Although lenalidomide is well tolerated in the majority of patients, possible side effects include pancytopenia, rash, and GI toxicities including diarrhea.[2,6] Lenalidomide-associated diarrhea can impact patient's quality of life and may lead to unnecessary dose reductions and discontinuation of therapy which can potentially compromise the disease outcome. Therefore, optimal management of the diarrhea is essential. In practice, loperamide and opioids have been used to treat lenalidomide-associated diarrhea, however, the clinical experience is that the effect of these medications is often suboptimal.
The incidence of lenalidomide-associated diarrhea, any grade, has been documented to occur in up to 25-40% of patients in treated with lenalidomide +/- dexamethasone in clinical trials (approximately 2-3% being grade 3 or 4 diarrhea).[1,2,9] In a recent meta-analysis including three major randomized controlled trials on lenalidomide maintenance, 2-3% of patients discontinued treatment due to diarrhea. There is currently limited information on outcomes in patients who discontinue lenalidomide maintenance due to diarrhea in comparison to those who continue. However, progression free survival and overall survival was longer in patients on lenalidomide maintenance versus those not on maintenance in a recent metaanalysis.[8]
In a recent a case series, 12 patients with lenalidomide-associated diarrhea were assessed to better understand underlying mechanisms of the diarrhea.[10] All patients underwent work up to exclude GI infections, lactose intolerance, celiac disease, inflammatory bowel disease, neoplasia, bacterial overgrowth, pancreatic insufficiency, and bile acid malabsorption. Selenium homocholic acid taurine (SeHCAT) scanning revealed severe bile acid malabsorption in 9 patients and mild bile acid malabsorption in 1 the 12 patients.[10] Thus, bile acid malabsorption was suggested as an underlying cause for lenalidomide-associated diarrhea.

Investigational drug colesevelam

Cholesterol is the major precursor of bile acid. Colesevelam (Welchol®) is a bile acid sequestrant which binds with bile acids in the intestine to form an insoluble complex that is eliminated in feces. The increased excretion of bile acids results in an increased oxidation of cholesterol to bile acid and a lowering of the serum cholesterol. Therefore, colesevelam has been FDA approved for lowering low-density lipoprotein (LDL) cholesterol and HbA1c in patients with primary hyperlipidemia and/or type 2 diabetes mellitus.

There is increasing data on the use of colesevelam in patients with diarrhea due to bile acid malabsorption in the setting of Crohn's disease and irritable bowel syndrome.[11,12] There are also anecdotal reports that suggest that patients with lenalidomide-associated diarrhea might benefit from dietary modifications and/or colesevelam.[10] In the above mentioned case series of 12 patients with GI symptoms (including diarrhea, urgency, fecal incontinence, and abdominal cramps) after starting lenalidomide; all patients were treated with low-fat diet and/or colesevelam. Two patients had improved symptoms on low-fat diet only. The remaining 10 patients were treated with colesevelam (+/- low-fat diet) in doses up to 6 tablets of 625 mg per day, split into doses with food and > 4 hours before or after lenalidomide administration. Of these 10 patients, 5 had normalization of bowel habits; the other 5 had improved symptoms with reductions in stool frequency and/or improvement in stool consistency.[10] In the case series of 12 patients, however, there is no information on severity (i.e. grade) of diarrhea, neither at baseline nor after intervention. The authors conclude that bile acid malabsorption is a major cause of lenalidomide-associated diarrhea and can be improved by using bile acid sequestrants such as colesevelam.[10] Confirmatory clinical trials are warranted to confirm the benefit of a bile acid sequestrant in lenalidomide-associated diarrhea.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single institution, single arm, open label phase II trial to evaluate the efficacy of colesevelam for myeloma patients on lenalidomide maintenance who experience grade 1 or more diarrhea. Patients will be given colesevelam at a starting dose of 2 tablets (2 x 625 mg) which can be increased to up to 6 tablets per day depending on efficacy and tolerability, see dose adjustment schedule section 9.2, page 16. Patients can continue on the study until unacceptable toxicity, diarrhea that remains grade 1 or higher at week 4, worsening of diarrhea at any point, or end of study (12 weeks), whichever comes first. Each patient will be followed for a total 12 weeks.

The primary endpoint of this study is improvement of diarrhea. Response is defined as improvement by at least 1 grade according to CTCAE version 5.0 (see page 15) or returns to patients baseline when receiving colesevelam. A total of 25 patients will accrue on the study in a Simon's two-stage minimax design. In the first stage of the study, 16 patients will accrue. If 1 or fewer patients have a reduction in diarrhea severity, the study will stop due to a lack of efficacy; otherwise, an additional 9 patients will accrue. We estimate that the accrual to the study will be approximately two patients per month. The study is expected to be completed in approximately two years.

A diarrhea diary will be filled out by patients to capture frequency and consistency of bowel movements. GI symptoms will be assessed using the GI oriented PRO-CTCAE questions. Diet will be recorded at several time points to assess changes in dietary intake prior to and while on colesevelam. Stool consistency will be assessed using the Bristol Stool Form Scale. Correlative studies include pharmacokinetic (PK) evaluation of lenalidomide as well as collection of stool for studies of the GI microbiome.

4.2 Intervention

All patients should be on maintenance single agent lenalidomide and experiencing grade 1 or higher diarrhea according to the CTCAE grading system. For treatment with colesevelam, the starting dose will be 1250 mg (2 x 625 mg) with food which can be increased to 6 tablets max per day based on efficacy and tolerability. Coleveselam should not be taken within 4 hours before or after lenalidomide and other interacting medications. All participants will be given a pill diary to record intake of colesevelam (Appendix 1). The effect of colesevelam on lenalidomide-associated diarrhea will be evaluated after 1, 2, 4, 12 weeks after start of treatment. If the diarrhea does not respond to the starting dose of colesevelam, the dose can be increased every 2 days to 2 tablets two times per day (2 x 625 mg BID) and later to 3 tablets two times per day (3 x 625 mg BID). The colesevelam dose can be decrease to 1 tablet per day if there has been improvement of diarrhea but emergence of side effects. Treatment with colesevelam will continue until drug-related toxicity, diarrhea that remains grade 1 or higher at week 2 despite dose elevations, or if worsening diarrhea occurs, or up to 12 weeks on study.

Patients will be evaluated by their physician and/or research nurse at baseline, after 1 week (+/- 2 days), after 2 weeks (+/- 2 days), after 4 weeks (+/- 7 days), and 12 weeks (+/- 7 days) for efficacy, toxicity, and compliance. The evaluations after 1, 2, and 4 weeks will preferably as office visits but can be replaced by telephone calls for sake of convenience.

Pharmacokinetics will be assessed in a subset of patients (up to 15 patients) at baseline and 8 days after start of colesevelam. All patients will be asked to participate in the PK studies and the first 15 who consent to this correlative part will be included. Research stool samples will be collected for all study participants at baseline and after 12 weeks of study.

Patients that repond to colesevelam can continue on the drug after the 12 weeks of study treatment. Coverage for colesevelam costs after the 12 weeks will not be covered by the trial but will go through patient's insurance.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

This study is IND exempt.

5.2 Colesevelam (Welchol®)

Welchol® (colesevelam hydrochloride) is a non-absorbed, polymeric, lipid-lowering and glucose-lowering agent intended for oral administration. Colesevelam hydrochloride is a high-capacity bile acid-binding molecule.

Colesevelam hydrochloride is poly (allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. The chemical name (IUPAC) of colesevelam hydrochloride is allylamine polymer with 1-chloro-2, 3-epoxypropane, [6- (allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride. The chemical structure of colesevelam hydrochloride is represented in the figure below.

Figure 1. Colesevelam chemical structure

Indications and Usage

Colesevelam is FDA approved for the indication of lowering LDL cholesterol and HbA1c in patients with primary hyperlipidemia and/or type 2 diabetes mellitus. Due to the bile acid binding effect, colesevelam has also been used for treatment of bile acid malabsorption in irritable bowel syndrome and inflammatory bowel disease.

Adverse Events

The most common adverse events during treatment with colesevelam include GI symptoms mainly constipation, dyspepsia, and nausea.[13] Hypoglycemia was observed in up to 3% of patients with diabetes mellitus. Several drug interactions were also observed, primarily with medication with a narrow therapeutic interval including oral anticoagulants and anticonvulsive drugs (see section 3.0, page 8).

Table 1. Potential adverse events with colesevelam

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Colesevelam, more than 4 and up to 100 may have: • Constipation • Dyspepsia (indigestion) • Nausea • Hypertension • Back Pain • Abdominal Pain • Infection • Headache
RARE, AND SERIOUS
In 100 people receiving Colesevelam, 3 or fewer may have: • Hypoglycemia (low blood sugar – symptoms include confusion, heart palpitations and shakiness)

Formulation

The Welchol tablet is an off-white, oval, film-coated, solid tablet containing 625 mg colesevelam hydrochloride. In addition, each tablet contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, silicon dioxide, HPMC (hydroxypropyl methylcellulose), and acetylated monoglyceride. The tablets are imprinted using water-soluble black ink.

Mechanism of Action

Colesevelam hydrochloride, the active pharmaceutical ingredient in Welchol®, is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption.

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.

Pharmacokinetics and Drug Metabolism

Colesevelam hydrochloride is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed. It is not metabolized systemically and does not interfere with systemic drug-metabolizing enzymes such as cytochrome P-450. In 16 healthy volunteers, an average of 0.05% of administered radioactivity from a single ^{14}C-labeled colesevelam hydrochloride dose was excreted in the urine.

Prescribing Information

Welchol (colesevelam) will be provided free of charge from Daiichi Sankyo, Inc. to the research subjects for 12 weeks durations only.

Administration

Patients should be advised to take Welchol® tablets with a meal and liquid. It can be taken to a maximum of 6 tablets once daily or 3 tablets twice daily.

Interactions

Colesevelam interacts with a number of drugs. Drugs with known interactions with colesevelam (cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan medoxomil, oral contraceptives [ethinyl estradiol, norethindrone], and metformin extended release) should be administered at least 4 hours prior to, or after colesevelam. Clinical trials and postmarketing reports in patients treated with colesevelam to reduce serum cholesterol include:

- Increased incidence of hypoglycemia in patients with diabetes mellitus
- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Administer phenytoin 4 hours prior to colesevelam.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin. Monitor INR.
- Elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy. Administer thyroid hormones 4 hours prior to colesevelam.

Drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to Welchol. Therefore in the published case-series, the investigators chose to separate lenalidomide administration from colesevelam administration by 4 hours. However, there is no information on potential effects of colesevelam on the absorption and pharmacokinetics of lenalidomide.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

Patients must meet all the following criteria to be eligible for treatment on study:

- Memorial Sloan Kettering Cancer Center (MSK) confirmed diagnosis of multiple myeloma
- Treatment with single agent lenalidomide maintenance
- Patient must be ≥18 years of age at the time of informed consent
- Experiencing grade 1 or more diarrhea according to the CTCAE 5.0 criteria for at least 4 out of 7 days preceding screening and study inclusion.
- Scheduled to receive lenalidomide maintenance cycles at MSK
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures

6.2 Subject Exclusion Criteria

- Patients with history of bowel obstruction
- Patients with serum triglyceride levels >300 mg/dL
- Patient with history of hypertriglyceridemia-induced pancreatitis
- Patients with known hypersensitivity to colesevelam or any component to the formulation
- Patients currently already receiving a bile acid sequestrant or have previously used bile acid sequestrant drugs for diarrhea and had no benefit
- Patients with diarrhea secondary to infection. Stool studies for GI pathogens should be collected prior to starting colesevelam but do not need to be resulted prior to starting Day 1 dose of colesevelam, unless infection is suspsected by the treating investigator, in which case *Clostridium difficile* PCR when clinically indicated, GI pathogen panel, stool ova and parasites, Giardia and Cryptosporum stool antigen tests will need to be resulted at investigator discretion.

7.0 RECRUITMENT PLAN

This study will be conducted at MSK. Efforts will be made to ensure that women and minority groups are adequately represented in this trial. All patients will be seen by MSK myeloma physicians and associated MSK co-investigators, enrolled and registered at MSK. All co-investigators agree to follow the treatment protocol and to conduct the proposed investigation according to recognized principles of good clinical practice. Participation is voluntary. Patients who report diarrhea while on lenalidomide maintenance will be approached and informed about the study by their physician. The Myeloma Service research nurses will then discuss the study details with patients and screen patients for eligibility. Every patient will be informed of the procedures to be followed, the potential benefits, side effects, risks, and discomforts of the trial and of potential therapeutic alternatives. All participants will be

required to sign statements of informed consent and research authorization that conform to FDA, IRB and HIPPA guidelines. Informed consent will be documented by the use of a written consent form approved by the MSK IRB.

8.0 PRETREATMENT EVALUATION

Evaluation of Inclusion and Exclusion criteria

The pretreatment evaluation can be done either during screening or up to 14 days before start of treatment on study or at baseline. In the event that the samples (stool studies to exclude GI pathogens and serum triglycerides) are taken at baseline, the patient can start study drug and will be taken off study if failure to fulfill inclusion criteria.

Grading of diarrhea as an adverse event is graded according to CTCAE version 5.0. To be eligible on the study, patients need to have grade 1 or more diarrhea according to the CTCAE definition. The CTCAE definition can be found at the National Institutes of Health website. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Table 2. Diarrhea grading according to CTCAE version 5.0

Grade	Description
Grade 0	No diarrhea present
Grade 1	Increase of <4 stools per day over baseline, mild increase in ostomy output compared to baseline
Grade 2	Increase of 4-6 stools per day over baseline, moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated

8.1 Physical examination

A complete physical examination will be performed during screening (<4 weeks prior to study enrollment). Physical exam will include:

- Abdominal examination
- Weight
- Height (at screening only)
- ECOG performance status

Abnormal physical examination findings during screening will be captured as medical history. Abnormal physical examination findings observed after signing of the informed consent will be recorded as adverse events (AEs).

8.2 Laboratory assessment

The following studies and laboratory tests will be completed within 0-14 days prior to colesevelam treatment:

- Complete blood count with differential count
- Comprehensive metabolic panel: sodium, potassium, chloride, carbon dioxide, serum creatinine, glucose, blood urea nitrogen (BUN), EGFR, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin, uric acid, LDH, total protein
- Serum protein electrophoresis (SPEP) and serum immunofixation to assess for presence and quantity of monoclonal protein (M-protein)
- Serum free light chain studies
- Quantitative immunoglobulins
- Serum triglycerides

8.3 Stool studies

Patients will have stool studies during screening (within 14 days before first dose of colesevelam)

Stool studies should include:

- Stool bacterial culture
- Stool *Clostridium difficile* toxin PCR when clinically indicated, thus in liquid but not formed stool samples.
- Stool ova and parasite examination
- Stool Giardia and Cryptosporidium antigen tests
- Stool sample collection for microbiota is optional if this is not already performed

Each physician should consider and rule out diarrhea cause by medications, especially if the medication has been started recently. Medications more likely to cause diarrhea include, magnesium-containing antacids and laxatives, sugar alcohols (e.g. mannitol, sorbitol, xylitol), antibiotics, metoclopramide, stimulant laxatives, acarbose, orlistat, metformin, immunosuppressants, and tricyclic antidepressants.

8.4 Diarrhea assessments

Diarrhea assessments using the CTCAE scale will be performed at screening (within 7 days before dosing on Cycle 1 Day 1). Diarrhea will be assessed using the CTCAE grading for the primary endpoint. Frequency and consistency of bowel movements will be recorded using a diarrhea questionnaire (Appendix 2). The Bristol Stool Form Scale will be used to evaluate diarrhea and stool consistency (Appendix 3).

8.5 Assessment of gastrointestinal symptoms and diet

GI symptoms will be assessed at baseline using the GI oriented questions within PRO-CTCAE (Appendix 4). Diet will be recorded using a dietary questionnaire (Appendix 5).

8.6 Correlative analyses: Pharmacokinetic studies

Blood samples will be collected from up to 15 subjects for determination of plasma concentrations of lenalidomide at baselines as well as day 8 while on colesevelam. Blood samples for the determination of plasma concentration of lenalidomide will be obtained from each patient via 6mL sodium heparin (green top) tube collected prior to the first dose of colesevelam at the following time points: pre- colesevelam (day 1 baseline lenalidomide PK), 2 hours post- colesevelam on day 1, then additional pre- and 2 hours- post colesevelam samples on day 8. The 2-hours post colesevelam samples are alotted a window of +/- 30 minutes. It is crucial the patient record the time of their most recent lenalidomide dose from the prior evening in order to provide an accurate time since dose for accurate PK comparisons both between historical lenalidomide PK controls and before vs after colesevelam. Bioanalytical measurements for lenalidomide will be conducted on an ultra HPLC-MSMS system using an assay developed and validated by the Clinical Pharmacology Program.

8.7 Correlative analyses: Gut microbiota and bile acid analyses

Stool samples will be collected from all patients at baseline and after 12 weeks of therapy. Samples will be stored for 16S rRNA sequencing and analysis of changes in gut flora that take place before and after use of colesevelam. Microbial ecology and metagenomic analysis will be performed using accepted computational methods to infer changes in gut microbiota throughout the study. Identification and quantification of bile acid species may be explored through use of liquid chromatography/ mass spectroscopy based approaches and/or metabolomics analyses.

9.0 TREATMENT/INTERVENTION PLAN

Colesevelam is FDA approved for lowering LDL cholesterol. Several studies have revealed that diarrhea induced by bile acid malabsorption can be improved with the use of colesevelam. Thus, this indication is considered routine. Furthermore, colesevelam has been indicated for lenalidomide-associated diarrhea, however, the effects are not well studied.

9.1 Treatment regimen

Only patients with grade 1 or more (CTCAE grading) diarrhea while on lenalidomide maintenance can initiate treatment with colesevelam on the study.

The treatment arm will be:

- The starting dose of colesevelam is 1250 mg (625 mg x 2) with food once daily and dose can be increased (6 tablets max per day) based on tolerability and efficacy
- Colesevelam should be spaced out from lenalidomide and other interacting medications by at least 4 hours

- Colesevelam is given continuously and patients will be treated for up to 12 weeks on study
- Treatment will continue until drug-related toxicity, worsening diarrhea, or unimproved diarrhea at 2 weeks despite increased dosage of the study drug or for a maximum of 12 weeks of treatment
- Patients who respond can continue on colesevelam after the 12 weeks of study treatment. Coverage for colesevelam costs after the 12 weeks will not be covered by the trial but will go through patient's insurance.

9.2 Dose adjustments

Colesevelam dosing can be adjusted based on tolerability and efficacy using Table 3. The dose of colesevelam can be increase or decreased at the invesitgator's discretion based on tolerability at any timepoint as long as changes and reason are documented. If Revlimid is held, colesevelam can be held at the same time.

Table 3. Dose levels and escalation/de-escalation for colesevelam

Dose level	Dosing of Colesevelam	Dose adjustment
0	1250 mg (2 tablets) daily	Starting dose
1	1250 mg (2 tablets) twice daily	Increase if diarrhea remains grade 1 or higher after 2 days on each dose level
2	1875 mg (3 tablets) twice daily	Increase if diarrhea remains grade 1 or higher after 2 days on each dose level
-1	625 mg daily	Decrease if improvement of diarrhea but emergence of side effects

Indications for discontinuation of study medication:

- If patients cannot tolerate dose level -1 then patients should discontinue treatment and come off study
- If patient has worsening of diarrhea within the first week after starting colesevelam, they should discontinue treatment and come off study
- If the diarrhea remains grade 1 or higher after 2 weeks of treatment

The investigator may *consider* withdrawing patients from the study for any of the following reasons:

- Side effects from colesevelam
- If there is protocol violation
- Non-compliance
- Administrative reasons
- Failure to return for follow-up

9.3 Concomitant medications

No other antidiarrheals will be allowed while on study treatment with colesevelam to evaluate efficacy accurately. If the diarrhea is worsening while on colesevelam, the patient will be

taken off study and can then start other anti-diarrheal medications. Similarly, if there is no sign of improvement after start of colesevelam despite dose escalation by 2 weeks, the patient will be taken off study and is allowed to start other anti-diarrheal medications.

Orally administered drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should be administered at least 4 hours prior to colesevelam. Therefore, lenalidomide should be spaced out from colesevelam by 4 hours at least. In addition, the physician should monitor drug levels of the co-administered drugs. Medications with known drug interactions are listed under section 5.0 page 11.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Physical examination

A complete physical examination will be performed during screening and at the end of trial (12 weeks +/-7 days).

Physical exam will include:

- Abdominal examination
- Weight
- Height (at screening only)
- ECOG performance status

Abnormal physical examination findings during screening will be captured as medical history. Abnormal physical examination findings observed after signing of the informed consent will be recorded as adverse events (AEs).

10.2 Laboratory assessment

Laboratory assessment will include:

- Complete blood count with differential count
- Comprehensive metabolic panel: sodium, potassium, chloride, carbon dioxide, serum creatinine, glucose, blood urea nitrogen (BUN), EGFR, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin, uric acid, LDH, total protein
- Serum protein electrophoresis (SPEP) and serum immunofixation to assess for presence and quantity of monoclonal protein (M-protein)
- Serum free light chain studies
- Quantitative immunoglobulins

Hematology and chemistry panels will be performed during screening, at 4 weeks (+/-7 days), and at the end of trial (12 weeks +/-7 days).

10.4 Diarrhea assessments (primary endpoint)

Diarrhea assessments using the CTCAE scale will be performed at baseline (day 1 of colesevelam), at 1 week (+/- 2 days), 2 weeks (+/- 2 days), 4 weeks (+/- 7 days), and at 12

weeks (+/- 7 days). The assessment on week 1, 2, and 4 can be carried out as a telephone call by the treating physician or research nurse for reasons of convenience. In this event, the information regarding response will be collected over the phone and questionnaires will be handed in or sent to MSK.

Frequency and consistency of diarrhea/bowel movements will be recorded using a diarrhea questionnaire (Appendix 2). This will be used to grade the diarrhea according to the CTCAE scale (CTCAE, see section 8.0, page 15).[14]

10.5 Symptom and diet assessments (secondary endpoints)

GI symptoms will be assessed at each follow-up (baseline; day 1 of colesevelam), at 1 week (+/- 2 days), 2 weeks (+/- 2 days), 4 weeks (+/- 7 days), and at 12 weeks (+/- 7 days) and will be instructed to fill in the GI oriented PRO-CTCAE questionnaire. The PRO-CTCAE for Gastrointestinal Symptoms is a 10-item multiple choice questionnaire using a 5-point Likert-type response format (Appendix 4). There is no composite score for this instrument. All items in this questionnaire will be analyzed individually.

Diet will be recorded using a questionnaire for dietary intake at set time points during the study (Appendix 5). In the diet questionnaire, patients will record their dietary intake at baseline and at the follow up at week 1, 2, 4, and 12 after starting colesevelam. We will record dietary intake and ask whether the patients have changed their diet as a results of the diarrhea and/or lenalidomide or colsevelam treatment.

Consistency of bowel movements will be graded using the Bristol Stool Form Scale which was developed for patient use.[3] Bristol Stool Form Scale categorizes stools into one of seven types based on stool consistency (Appendix 3).

These questionnaires together take between 10 and 20 minutes to complete. These instruments will be given to the patient at the start of the study and will be handed in at clinical visits or can be sent to MSK in the event that visits are replaced by a phone call (see section 4.2).

10.6 Correlative analyses: Pharmacokinetic studies

Blood samples will be collected from up to 15 subjects for determination of plasma concentrations of lenalidomide while on colesevelam the following time points:

- Pre- and 2 hours post the 1st dose of colesevelam – considered day 1
- Pre- and 2 hours post the colesevelam dose on day 8 (± 2 days) of colesevelam

10.7 Correlative analyses: Gut microbiota and bile acid analyses

Stool samples will be collected from all patients at baseline and after 12 weeks of colesevelam therapy.

10.8 Toxicity

All adverse events, including laboratory abnormalities, will be collected, recorded, and graded according to the National Cancer Institute (NCI) CTCAE, version 5.0.

10.9 Compliance

Patient's medication compliance will be evaluated by using medication logs/diaries where patient will document when and how often they use either medication each day (Appendix 5). They will bring in medication log/diary at every clinic visit.

10.10 Table 4. Overview of time points for sampling and clinical assessment

	Baseline	**Cycle 1 Day 1 (Within 14 days of baseline)**	**Cycle 1 Day 8 (+/-7 days)**	**Cycle 1 Day 15 (+/-7 days)**	**4 weeks/ End of Cycle 1 (+/- 14 days)**	**12 weeks / End of Cycle 3 (+/- 21 days)**
MD/RN assessment	Visit		Visit or telephone assessment	Visit or telephone assessment	Visit or telephone assessment	Visit
Stool studies GI pathogens [a]	X[a]					
Triglycerides	X					
CBC	X					X
Comp	X					X
SPEP, IFE and FLC	X					X
Stool Diary (response assessment) and Bristol Stool Scale [b]	X		X	X	X	X
PRO-CTCAE	X		X	X	X	X
Nutritional Survey [c]						X
PK studies [d]		X[d]	X[d]			
Research stool samples [e]	X					X

a. Stool studies for GI pathogens should be collected prior to starting colesevelam but do not need to be resulted prior to starting Day 1 dose of colesevelam, unless infection is suspsected by the treating investigator.

b. Response assessments (Stool diaries) will be done at Cycle 1 Day 8, Cycle 1 Day 15, end of Cycle 1 (week 4) and end of Cycle 3 (week 12). If diarrhea does not improve by at least 1 grade from baseline (using CTCAE version 5.0) or to patient's baseline bowel pattern by the end of Cycle 1 they will be removed from study.

c. Patients will complete one nutrtional survey ("Food and Activitity Questionaire" survey will be used) and return at week 12 visit.

d. Lenalidomide pharmacokinetics will be assessed in up to 15 patients to assess possible drug interactions between lenalidomide and colesevelam. In these patients, a blood sample will be drawn pre- and 2 hours post the first colesevelam dose (day 1), as well as pre- and 2 hours post colesevelam on day 8 after initiation of colesevelam.

e. Research stool samples will be collected at baseline and after 12 weeks of treatment for microbiota and bile acid studies.

11.0 TOXICITIES/SIDE EFFECTS

Colesevelam (Welchol®) is provided to investigator by Daiichi Sankyo, Inc.

In clinical trials, the most common side effects with colesevelam (incidence ≥ 2% greater than placebo) include constipation, dyspepsia, and nausea. In trials including patients with diabetes, the overall incidence of hypoglycemia was 3.0% in colesevelam-treated patients and 2.3% in placebo-treated patients.
Postmarketing reports with concomitant colesevelam administration include drug interactions with phenytoin, warfarin, and thyroid hormone replacement therapy (section 3.0, page 9). These medications should be administered >4 hours prior or after colesevelam and the serum concentration and therapeutic effect should be monitored. Other postmarketing reports include bowel obstruction, dysphagia, esophageal obstruction, fecal impaction, hypertriglyceridemia, pancreatitis, and increased transaminases.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response is defined as improvement in diarrhea by 1 grade according to the CTCAE 5.0 scale or returns to patients baseline. Resolution of diarrhea is defined as normalization of bowel habits (grade 0). Response grading according to CTCAE 5.0 definition will be assessed at baseline and after 1 week, 2 weeks, 4 weeks and the end of study at 12 weeks. When evaluating the primary endpoint based on CTCAE 5.0, the grading will be determined by recalling the average number of stools in the previous two days. In addition, GI symptoms and diet will be assessed and at baseline and after 1 week, 2 weeks, 4 weeks and at the end of study at 12 weeks.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

The investigator is *required* to withdraw patients from the study for any of the following reasons:

- If at any time a patient develops unacceptable toxicity from colesevelam
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

- If there is no resolution of diarrhea to grade 0 at 2 weeks after the dose has been increased to dose level 2

The investigator may *consider* withdrawing patients from the study for any of the following reasons:

- Side effects from colesevelam
- If there is protocol violation
- Non-compliance
- Administrative reasons
- Failure to return for follow-up

14.0 BIOSTATISTICS

Primary Objective:
This is a phase 2, open label, single arm study to evaluate the efficacy of colesevelam to improve lenalidomide-associated diarrhea in patients with multiple myeloma treated with lenalidomide maintenance. There is limited data on the resolution of lenalidomide-associated diarrhea in this patient population. However, if 10% or less of patients have an improvement by 1 grade or returns to patients baseline when receiving colesevelam within the first 4 weeks or starting colesevelam, the intervention will not be considered promising. If 30% of patients or more have a reduction to grade 0 diarrhea or returns to patient's baseline, the intervention will be considered promising and worthy of further investigation. The intervention will be considered a success if at any point the patient had an improvement to grade 0 diarrhea or returns to patients baseline within the first 4 weeks or starting colesevelam. Based on these rates, a Simon two-stage minimax design will be employed. In the first stage of the study, 16 patients will accrue. If one or fewer patients have a reduction in diarrhea severity, the study will stop due to a lack of efficacy; otherwise, an additional 9 patients will accrue. If at the end of study more than 4 out of the 25 total patients have a reduction in diarrhea to grade 0 or to patient's baseline by the week 4 evaluation, the study will be considered promising. The type I and type II errors are both set at 0.10.

Patients who are removed from study before the 1-week evaluation for reasons unrelated to worsening of diarrhea, or drug-related toxicity will be considered nonevaluable and will be replaced for the primary analysis. Patients removed from study for worsening of diarrhea, a lack of improvement in diarrhea, or drug-related toxicity within the first 4 weeks of the study will be considered treatment failures.

Secondary Objectives:
- GI symptoms will be evaluated throughout the study using the PRO-CTCAE questionnaire for GI symptoms. This questionnaire will be evaluated at baseline and weeks 1, 2, 4, and 12. Individual components of the PRO-CTCAE GI will be summarized longitudinally for each patient.
- Patient's dietary intake will be recorded with the aim of assessing whether patients have changed their diet due to the diarrhea and whether patients go back to their normal diet if

the diarrhea responds to colesevelam. The proportion of patients who have had a change in their diet due to diarrhea, and the proportion who had a diet change due to either lenalidomide or colesevelam will be reported

- Patient diarrhea will be further summarized during the study period using the Bristol Stool Form Scale. The scale has seven types of stool consistency. The proportion of patients with improvements in stool consistency from baseline to weeks 1, 2, 4, and 12 will be calculated along with a 95% exact confidence interval.
- The proportion of patients with sustained response by week 12 (end of study) will be calculated with a 95% exact confidence interval. This is calculated as the proportion of patients who have grade 0 diarrhea at week 12 among patients who achieved grade 0 diarrhea by the week 4 assessment.

Correlative studies

Lenalidomide pharmacokinetics while on colesevelam will be described in up to 15 patients treated on this study; the changes from baseline will be reported.

Stool samples will be analyzed for changes in gut microbiota that take place before and after 12 week of colesevelam treatment. Changes in alpha diversity will be summarized using average change in the Inverse Simpson index. Microbial ecology and metagenomic analysis will be performed to describe changes in gut microbiota throughout the study.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

There is no randomization in this clinical trial.

16.0 DATA MANAGEMENT ISSUES

All patients will be enrolled on protocol at Memorial Sloan Kettering Cancer Center. We expect to be able to enroll the necessary 25 patients into this study in 2 years.

The data manager (Clinical Research Associate, CRA) will be responsible for confirming eligibility and assisting the physician with the registration process. All study data will be collected by an assigned CRA who will enter this information into the Clinical Research Database (CRDB). This database will be utilized for data collection and storage and for reporting protocol specific events such as accrual demographics, toxicities and adverse events to the IRB, and the sponsor.

The CRA will collect toxicity and concomitant medication information and patient interviews. Adverse events, including all toxic effects of treatment will be tabulated individually according to severity or toxicity grade. The data manager will also monitor laboratory testing throughout the study. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSK specified normal ranges.

16.1 Quality Assurance

Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored,

in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSK and collaborating centers IRB guidelines. Patients will be eligible for this trial regardless of gender or racial/ethnic background.
No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative.
A copy of the signed informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the investigator.
The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Potential risks and benefits

The potential risks of this therapy may outweigh the potential benefit in an individual patient. The potential risks to patients are related to drug induced adverse effects and are outlined in Section 11.0. Appropriate exclusion criteria for patients are listed in Section 6.0: Patient Eligibility. Appropriate exclusion of patients with significant organ dysfunction or infection will help avoid treatment-related toxicity. Careful monitoring of laboratory parameters and patient symptoms, along with serial assessment for disease recurrence, will be carried out routinely in order to minimize the risk of adverse effects during this study.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

All records identifying the subject will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available. Study data stored on a computer will be stored in accordance with local data protection laws and regulations.

Subjects will be informed in writing that representatives of IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations. If the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations and according to the terms and agreed upon in such subjects' signed consent forms.

The consent indicates that individualized de-identified information collected for the purposes of this study may be shared with other qualified reseearchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient of participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/ intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test of procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

Reports of SAEs/pregnancies/lactation must be reported to DSI CSPV, as outlined in the current version of the Investigator Initiated Study Grant between Daiichi Sankyo Inc. and MSKCC.

The report should contain the following information:

- The date the adverse event occurred

- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the adverse event was expected
- Detailed text that includes the following
    - An explanation of how the adverse event was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded rather than the individual signs or symptoms of the diagnosis or syndrome. An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms. All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of investigational product (IP) and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded in the subject's source documents.

Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);

- Is a congenital anomaly/birth defect;
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event. The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as “serious” which is based on subject/event outcome or action criteria associated with events

that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory obligations.

Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: Means a causal relationship of the adverse event to IP administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: Means there is a reasonable possibility that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention;
- or is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event. If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis

or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

17.2.1

Not applicable.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1 Colesevelam pill diary
Appendix 2 Diarrhea questionnaire
Appendix 3 Bristol Stool Scale
Appendix 4 PRO-CTCAE