# Efficacy of Curcumin and Piperine in Patients on Active Surveillance for either Monoclonal Gammopathy of Unknown Significance (MGUS), low-risk Smoldering Multiple Myeloma (SMM) or Early Stage Prostate Cancer: A Pilot Study

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## ABBREVIATION LIST

| | |
|---|---|
| MIC-1 | Macrophage Inflammatory Cytokine-1 |
| AS | Active Surveillance |
| PSA | Prostate Specific Antigen |
| BPH | Benign Prostate Hypertrophy |
| IU | International Units |
| mL | Milliliter |
| MGUS | Monoclonal Gammopathy of Unknown Significance |
| SMM | Smoldering Multiple Myeloma |
| MM | Multiple Myeloma |
| FLC | Free Light Chains |
| SPEP | Serum Protein Electrophoresis |

## STUDY SUMMARY

| | |
|---|---|
| Title | Efficacy of Curcumin and Piperine in Patients on Active Surveillance for either Monoclonal Gammopathy of Unknown Significance (MGUS), low-risk Smoldering Multiple Myeloma (SMM) or Early Stage Prostate Cancer: A Pilot Study |
| Short Title | Curcumin in MGUS, SMM or Prostate Cancer |
| Phase | Pilot |
| Methodology | Open-Label |
| Study Duration | 2 year |
| Study Center | Wilmot Cancer Institute |
| Objectives | Primary Objective: To determine the biochemical response rate of Curcumin & Piperine supplementation in patients on AS for either early stage prostate cancer, SMM or MGUS.<br><br>Secondary Objectives: 1) To investigate the association of MIC-1 with disease response and to determine if curcumin and Piperine supplementation can delay time to active treatment and, 2) To bank serum and urine samples for future testing of potential alternative biomarkers. |
| Number of Subjects | 40 (20 prostate cancer, 10 MGUS and 10 SMM) |
| Diagnosis and Main Inclusion Criteria | Subjects with early stage prostate cancer, MGUS or SMM whom have chosen Active Surveillance as their treatment choice. |
| Study Product(s), Dose, Route, Regimen, Duration | All patients will receive an over-the-counter supplement consisting of Curcumin plus Piperine 2 gm/ 10mg(two tablets) orally twice daily for 12 months. |

## 1.0 BACKGROUND AND RATIONALE

### 1.1 Background:

Prostate cancer (PC) is one of the most common cancers in men. The global burden of this disease is rising. Its incidence and mortality rates are higher in certain populations such as African American (AA) men compared to white men and other ethnic groups. This disparity may be in part associated with nutritional factors and studies have suggested a potential preventative and therapeutic effect of curcumin (1,2).

Multiple myeloma (MM) is the second most common hematologic malignancy amongst Caucasian Americans, but a greater incidence of MM amongst AAs makes it the most common hematologic malignancy amongst AAs. MM is an incurable hematologic malignancy that is characterized by multiorgan involvement and is associated with significant morbidity and mortality. Myeloma defining events include hypercalcemia, renal failure, anemia, and lytic bone lesions (CRAB criteria), involved serum free light chains >100mg/dL, serum free light chain (sFLC) ratio >100, and/or presence of ≥ 60% monoclonal plasma cells in the bone marrow. MM is thought to be preceded by MGUS or SMM in most cases (3). The majority of patients with MGUS and SMM do not go on to develop MM, but a subset of these patients do progress to having symptomatic disease and tolerable, low-risk treatment options to prevent disease progression are needed. The increased incidence of MM in AAs can be traced to an almost doubled incidence of MGUS amongst AAs, but the reasons for this disparity are not known. While biology may play a role, dietary differences is also being explored as disparate contributors to disease burden amongst plasma cell dyscrasias.

Prostate cancer and MM are both diseases with an increased incidence amongst AAs, but also uniquely each have an asymptomatic or precursor stage representing a unique opportunity to investigate the impact of nutritional factors on ultimate emergence of symptomatic cancers requiring treatment.

Active surveillance (AS) has become a standard of care for patients with ≤ Gleason's 6 adenocarcinoma of the prostate and selected patients with Gleason's 7 disease. The optimal approach to monitoring these patients, though, has not been well defined and remains a subject of extensive investigation. Serial biopsies have been the standard but optimal biopsy frequency is unclear. As an alternative, multiparametric MRI (Mp-MRI) has become increasingly utilized as an assessment for disease progression (4). One recent series suggested that standard serial re-biopsies might be waived if follow-up Mp-MRIs are stable. In that study over 60% of patients with signs of tumor progression on Mp-MRI during AS had a Gleason's Score upgrade on re-biopsy. There are concerns though regarding potential variability in Mp-MRI performance across different institutions and that it has had a relatively low positive predictive value (5). Therefore, the role of Mp-MRI continues to need to be defined and its use incorporated in conjunction with repeat prostate biopsies, novel biomarkers, and other assessment tools.

Smoldering myeloma is an asymptomatic disease that requires the absence of myeloma defining events and the presence of between 10-60% clonal plasma cells in the bone marrow. While these patients are asymptomatic, they carry a lifetime risk of progressing to the incurable malignancy, multiple myeloma. The average risk of progression from SMM to MM is also variable based on risk factors (6). A revised risk stratification system identified high risk of progression in patients with a paraprotein of at least 2g/dL, serum

free light chain ratio of ≥ 20, and bone marrow clonal plasma cells ≥ 20% identifies patients with up to a 75% risk of progression in 5 years(7).

The historic standard of care for patients with MGUS and SMM is observation because early studies failed to demonstrate a survival advantage and the risk of toxicity has outweighed the benefit of treatment for a group of patients that may never progress to MM (8-10). Interventional studies of MGUS are limited by the number of patients needed to demonstrate a benefit amongst a relatively low-risk population and by a low tolerance for toxicity or long-term side effects. In SMM, our recent risk-stratification systems have allowed us to identify and better study those patients with the highest risk of progression in SMM. Two randomized trials have looked at the use of lenalidomide or lenalidomide + dexamethasone versus observation alone in patients with intermediate or high risk SMM, but excluded patients with low risk SMM with a lower risk of disease progression (11). Both trials demonstrate improved PFS for the lenalidomide containing arm, but OS was improved only in the lenalidomide + dexamethasone arm. Concerns over the long-term impact of early intervention, trial design, inclusion criteria, and optimal intervention have limited the adoption of such strategies in clinical practice. The current standard of care remains observation for patients with MGUS and SMM. A low-risk, well-tolerated treatment option demonstrating anti-myeloma activity has the potential to save lives and dramatically change the paradigm of treatment for plasma cell disorders.

Curcumin, a phenolic compound originally derived from the turmeric plant is a widely known spice. Multiple preclinical studies have demonstrated its efficacy in inhibiting proliferation and metastasis as well as enhancing cell cycle arrest or apoptosis in various types of cancer cells. Studies have described the ability of curcumin to suppress prostate carcinoma cells by interacting with different molecular targets including p53, Ras, PI3K/Akt, Wnt/beta-catenin and mTOR (12,13).

In several clinical trials, curcumin has been proven safe with a low toxicity profile and limited side effects regardless of the dosage. It has been categorized as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (USFDA), with recommended serving dose ranging from 8 g/day to 12 g/day.

Curcumin has been studied as a potential prostate cancer preventive agent in a randomized double-blind placebo-controlled clinical trial involving 85 participants who had prostate biopsies but had neither prostatic intraepithelial neoplasia nor prostate cancer. After six months of daily intake of curcumin in combination with isoflavones, the combination was found to significantly reduce PSA serum levels in the of participants who had a serum PSA level ≥10 µg/ml in the supplement-treated group compared with that of the placebo. In a separate study, the supplementation of 3 g per day of curcumin for 3 months has been reported to increase plasma total antioxidant capacity significantly among 40 patients treated with radiotherapy for prostate cancer (14).

A prospective randomized phase III trial (ClinicalTrials.gov Identifier: NCT02064673) is ongoing now to compare the effect of adjuvant supplementation of curcumin 500 mg twice a day for 6 months on recurrence-free survival as compared to placebo in the treatment of 600 prostate cancer patients after radical prostatectomy. An additional randomized, double-blind, placebo-controlled trial was performed on patients with prostate cancer who received intermittent androgen deprivation (IAD). Participants who finished the first on-treatment period of IAD were randomized into a curcumin or placebo group. The patients took oral curcumin (1440 mg/day) or placebo for six months and were followed up until the

beginning of the second time back on treatment. A total of 97 participants were randomized 1:1 to curcumin (n = 49) and placebo (n = 48) groups. Six months' intake of oral curcumin at this dose did not significantly affect the overall off-treatment duration of IAD, however, PSA elevation was suppressed with curcumin intake during the curcumin administration period (15).

The biggest challenge to achieve desirable anticarcinogenic effects of curcumin has been its bioavailability, which cannot be overcome just by increasing the dose or frequency of administration. The majority of clinical trials to date have been done with curcumin alone but some suggests suggest the addition of Piperine may improve efficacy. Piperine appears to significantly increase the absorption, serum concentration and bioavailability of Curcumin in humans up to 20-fold when they are given concomitantly (16).

Piperine is a major bioactive alkaloid that is present in the black pepper. In human prostate cancer cell lines and animal models, piperine has been reported to promote autophagy, induce cell cycle arrest at $G_0/G_1$ via down-regulation of cyclin D1 and cyclin A and up-regulation of p21 and p27. It triggers apoptosis and inhibits the growth and proliferation of both androgen-sensitive and androgen-insensitive prostate tumors in a dose-dependent manner. It has also been shown to inhibit expression of nuclear factor-kB (NF-kB) transcription factor and down-regulate phosphorylated STAT-3. Additionally, in a xenograft models of human castration-resistant prostate cancer, piperine and docetaxel in combination have been reported to remarkably enhance the anti-tumor effectiveness of docetaxel (16).

PSA has not been a reliable indicator of disease progression in the setting of AS and we need novel biomarkers. Macrophage inhibitory cytokine (MIC-1) is a member of the transforming growth factor (TGF)-super family, and is known to be expressed in a variety of human tumors. MIC-1 has drawn significant attention due to its increased association with the development and progression of prostate cancer and increasing serum MIC-1 levels correlate with the presence of bone metastasis. In one study, 240 serum samples from prostate cancer, BPH and control subjects were evaluated for the expression of MIC-1. The expression level of MIC-1 was significantly higher in prostate cancer than in controls or BPH patients. Regression analysis revealed a significant correlation between MIC-1 vs. PSA ($r = 0.09$; $p < 0.001$) and MIC-1 vs. GS ($r = 0.7$; $p < 0.001$) with analysis suggesting that the MIC-1 was better than PSA (17,18).

Amongst plasma cell dyscrasias, curcumin and piperine have also been shown to have anti-MM activity. Curcumin has been shown to have anti-neoplastic activity through its ability to modulate several signaling pathways essential in cell proliferation and apoptosis. Specifically, it has been shown to downregulate the nuclear factor kappa B (NF-κB) pathway, and interleukin-6/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathways, in multiple myeloma cell lines(19). Whole exome sequencing efforts have shown that patients with MGUS and SMM have a lower mutational burden overall and fewer mutations along the NF-κB pathway, suggesting that these patients may have disease biology that is more susceptible to intervention along this pathway.

Numerous preclinical and mouse model studies have demonstrated the ability of curcumin to induce apoptosis in malignant plasma cells and to work synergistically with proteasome inhibitors and immunomodulatory agents to potentiate the effects of standard anti-myeloma therapy (20-24). Curcumin sensitivity testing in 29 human myeloma cell lines

revealed high sensitivity of cell death induction in t (4;14) and t (14;16) cell lines, and intermediate sensitivity in t (11;14) cell lines, both independent of *TP53* mutation status, indicating promise in even higher risk disease (25)

In a prospective, single-blind, crossover study, 26 patients received 4g oral curcumin daily and had urine and blood samples collected for measurement of serum paraprotein and urinary N-telopeptide of type I collagen (26). The study showed that oral curcumin was able to decrease paraprotein by 12-30% in patients who had a paraprotein level of >0.2g/dL. A randomized, double-blind, placebo-controlled cross-over study was conducted to study the effect of curcumin on sFLC response and bone turnover in the patients with MGUS and SMM (27). Patients received either curcumin 4g or placebo 4g and crossed over after 3 months, with an option to enter into an open-label 8g dose extension study. They found that curcumin was associated with decreased sFLC ratio, involved free light chain level, difference between involved and uninvolved serum free light chains, as well as urinary deoxypyridinoline, a marker of bone resorption. Curcumin with piperine in combination has been used in a clinical trial which investigated the safety of curcumin alone or in combination with piperine in myeloma patients at escalating doses (19). At the highest dose level of curcumin 12g/day divided in 2 equal doses combined with 10 mg piperine supplement, patients had no significant adverse effects. Additionally, this combination was found to significantly downregulate NF-κB (77%, $p<0.0001$), STAT3 (69%, $p<0.001$), and decrease expression of COX2 (66%, $p<0.0001$). This has highlighted the potential therapeutic benefit of this combination in reducing risk of disease progression and promoting disease stability.

We therefore propose a study investigating the use of curcumin and piperine in patients with MGUS, low-risk SMM, and prostate cancer undergoing AS to determine the tolerability of this combination and rate of biochemical response. The rationale for studying this combination in patients with prostate cancer as well as MGUS and SMM is supported by the reliance of both disease processes on the NF-κB and the PI3K/Akt/mTOR signaling pathways, which are downregulated by curcumin, for proliferation and progression of disease(28,29) The NF-κB pathway is constitutively active in prostate cancer and is involved in regulation of androgen receptor expression and evolution of disease (30) Similarly, this pathway is constitutively active in MM cell lines and inhibition has been shown to induce apoptosis (31) A study comparing MGUS patients to healthy individuals found increased circulating markers of bone turnover including soluble receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin, and macrophage inflammatory protein 1-alpha (MIP-1a), suggesting increased osteoclastogenesis compensated by bone formation in this early precursor disease (32). MIC-1 expression has been associated with promotion osteoclastogenesis in MM and formation of bone metastases in prostate cancer, and thus may be a useful marker of subclinical disease progression or response in both of these disease processes (33).

## 1.2 Preliminary Data

In a pilot study (34), we examined if serum or urine MIC-1 provides any predictive capability for the severity of prostate cancer in pre-surgical diagnosed males. Samples from 40 Caucasians and 40 AA men were analyzed for serum MIC-1 level in addition to a limited (n =10-17) number of urine samples by sandwich ELISA. Differences between AA and Caucasians were identified using Wilcoxon tests for continuous variables and Fisher exact tests for categorical variables. Pearson's correlation coefficient, univariable linear

regression, and analysis of covariance were used to identify significant associations between continuous outcomes and differences among races. Highly significant differences between the two races were found in MIC-1 ($p = 0.0001$) and Gleason scores ($p = 0.0009$), with AA having higher MIC−1 expression (Median 1220.4 versus 790.8) and Gleason scores (Median 7 versus 6) than Caucasians, on average. PSA was also significantly higher in AA (Median 6.72 versus 6.35, $p = 0.04$) men. No differences in age or stage of disease were detected between groups ($p > 0.05$). In Caucasians, MIC-1 expression was positively associated with PSA ($p < 0.01$), and age ($p < 0.0001$), while Gleason score was positively associated with PSA ($p < 0.05$) and age ($p < 0.05$). Thus, higher levels of MIC-1 expression and higher Gleason scores were associated with older patients when limiting our sample to Caucasians. In AA, however, both older and younger patients had highly expressed MIC-1 and high Gleason scores. Interestingly, urine MIC-1 levels were significantly higher in AA men with prostate cancer than Caucasian patients, and appeared to be more sensitive and specific. These observations indicate that addition of MIC-1 may help to improve the diagnostic capability of an aggressive stage of prostate cancer at least in African American men. High urine MIC-1 in AA men with prostate cancer may indicate MIC-1 is a potential biomarker for aggressive prostate cancer as often seen in AA men at the time pf diagnosis. Additional testing is need in both Caucasian and AA men to see if MIC-1 could help predict disease aggressiveness, and therefore help identify which patients are more likely to progress on AS.

We plan to evaluate the efficacy of curcumin and piperine in patients on AS for their early stage prostate cancer, MGUS, or low-risk SMM; and determine the effectiveness of serum and urine MIC-1 levels in monitoring disease response and/or progression as correlated with PSA and FLC/ SPEP. Serum and urine samples will also be stored with the plan to test for potential alternative biomarkers. The results from this pilot study will provide additional preliminary data in support of funding for a planned larger, randomized study in AS for prostate cancer which will also incorporate Mp-MRI.



## 2.0 STUDY OBJECTIVES

**2.1.1** Primary Objective: To estimate the response rate of curcumin and piperine supplementation at a dose of 2 gram/10mg(two tabs) BID in early stage prostate cancer patient undergoing active surveillance or patients on observation for MGUS/ low-risk smoldering myeloma. The response rate of interest in prostate cancer patients is biochemical response as measured by PSA. The response rate of interest in MGUS/ low-risk SMM is at least partial response as graded by IMWG response criteria (see appendix 1). ***Hypothesis: Curcumin plus piperine supplementation will decrease disease burden as measured by PSA, FLC, or SPEP. Benchmark for success: A 20% or higher response rate in either cohort would be considered worthy of pursuing in future studies.***

**2.2 Secondary Objectives:** 1) To determine PFS and time to treatment for patients receiving curcumin and piperine, 2) To confirm the safety and tolerability of curcumin in combination

with piperine. 3) To bank serum and urine specimen for future testing of alternative biomarkers.

**2.3** **Exploratory objective:** To explore the association of serum and urine MIC-1 levels with disease progression in patients undergoing either AS for treatment of their prostate cancer or their MGUS/low-risk SMM**.**

2.4 **Endpoints:** Primary Endpoint: Response rate after 12 months of curcumin plus piperine supplementation. Biochemical response rate for Prostate Cancer will be defined as at least a 50% reduction in PSA level after 12 months of curcumin plus piperine. Response rate for MGUS/low-risk SMM will be defined as at least partial response (PR, VGPR, CR, or sCR) as defined by IMWG response criteria (Appendix 1).

## 3.0 SUBJECT ELIGIBILITY

**3.1** **Inclusion Criteria:** Subjects must meet all of the inclusion criteria to participate in this study.

**3.1.1** The patient must provide study-specific informed consent prior to study entry.

**3.1.2** Age ≥ 18 years of age.

**3.1.3** Subjects with either 1) non-metastatic biopsy proven adenocarcinoma of the prostate who have chosen AS the treatment option for their prostate cancer or 2) have the diagnosis of either MGUS or low-risk SMM and are currently on observation alone.

**3.1.4** For patients with MGUS or low-risk SMM, diagnosis must be according to the definition of the International Myeloma Working Group (IMWG).

**3.1.4.1** MGUS: serum M-protein <3.0g/dL, <10% clonal plasma cells (PCs) in the bone marrow, and absence of end-organ damage (CRAB criteria) that can be attributed to the plasma cell disorder.

**3.1.4.2** SMM: serum M-protein of $\geq$ 3.0g/dL or a proportion of clonal PCs in the BM of $\geq$ 10% but $<$ 60%, and no evidence of end organ damage as described below.

Absence of end organ damage is defined by absence of CRAB criteria and not meeting criteria for MM by light chains (free light chains ≥100 and involved light chain ≥100mg/L) :
**C**: Absence of hypercalcemia, defined as calcium $\leq$ 11mg/dL.
**R**: Absence of renal failure, defined as serum creatinine $\leq$ 2.0mg/dL and creatinine clearance ≥ 40mL per min.
**A**: Absence of anemia, defined as hemoglobin $\geq$ 10g/dL.
**B**: Absence of lytic bone lesions per IMWG recommendations: One of either PET-CT, low-dose whole-body CT, or whole-body MRI. Increased uptake on PET-CT alone is not adequate for the diagnosis of multiple myeloma; evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination.

**3.1.4.2.1** Nor more than one of the risk factors below that portends for an increased risk of progression to MM:

- Abnormal serum free light chain ratio.
- M-spike ≥ 2.0g/dL.
- ≥ 20% bone marrow clonal plasma cells.
- Immunoparesis ≥ 20% reduction from institutional normal standard of uninvolved immunoglobulins.

**3.1.5** Karnofsky performance status (KPS) of ≥ 70%.

**3.1.6** Patients with prostate cancer must have a serum creatinine of < 2.0mg/dl.

**3.1.7** Patients must not have any known bleeding diathesis and must not have taken therapeutic levels of any anticoagulant or antiplatelet agents within 7 days prior to starting treatment. Prophylactic doses of aspirin (81mg daily) is allowed.

**3.1.8** Patients must have a baseline INR and PTT which is within normal limited within 30 days of starting treatment.

**3.1.9** Patients must be able to swallow pills.

### 3.2 Exclusion Criteria

**3.2.1** Currently taking supplements containing either curcumin or piperine.

**3.2.2** Any history of an allergy to curcumin or piperine.

**3.2.3** Plan to start any additional over the counter supplements during trial period.

**3.2.4** For prostate cancer patients must not be planning to undergo primary curative therapy for their prostate cancer (radiation, surgery, brachytherapy).

**3.2.5** For MGUS/ SMM patients, must not have had evidence of disease progression which might require treatment during the one-year study period.

**3.2.6** Other: symptomatic plasma cell leukemia, multiple myeloma, amyloidosis, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein).

**3.2.7** Subject is pregnant or breast feeding, or planning to become pregnant during the treatment period. For both male and female participants, highly effective contraceptive methods are required for the duration of study treatment.

**3.2.8** Evidence of any of the following conditions per subject self-report or medical chart review:

- Major surgery or significant traumatic injury occurring within 4 weeks before enrollment.

## 4.0 TREATMENT PLAN

### 4.1 Treatment Dosage and Administration

Curcumin plus Piperine **(**Curcumin C3 Complex®**)** at a dose of 2 gram/10 mg (two tablets) orally BID for 12 months.

### 4.2 Toxicities and Dosing Delays/Dose Modifications

Curcumin with piperine is a well-tolerated over-the-counter supplement with minimal to no expected toxicity. In several clinical trials, curcumin has been proven safe with a low toxicity profile and limited side effects regardless of the dosage (14,15). It has been categorized as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (USFDA), with recommended serving dose ranging from 8 g/day to 12 g/day. The most common side effects observed in clinical studies are gastrointestinal and include constipation, dyspepsia, diarrhea, distension, gastroesophageal reflux, nausea, vomiting, yellow stool and stomach ache. Curcumin has been shown to have an antiplatelet effect and, along the reported risk is very low, there is a potential bleeding risk, especially when given in combination with an anticoagulant or antiplatelet agent.

Patients who experience a Grade 1 or 2 toxicity requiring a treatment break can stop study supplement until recovery to grade or resolution. Dose should then be decreased to 1 gram/5 mg(one tablets) BID.

Any patient who has a Grade 1 or 2 toxicity requiring longer than a two-week treatment break should be removed from study. Any patient experiencing a Grade 3 or higher toxicity should also be removed from study.

Any patient with prostate cancer who chooses to pursue curative treatment during the study or progresses to where standard guidelines recommend curative intervention, will be removed from the study. Any patient with either MGUS or low risk smoldering MM who progresses to either active MM or a higher risk smoldering MM will be removed for the study.



### 4.3 Concomitant Medications/Treatments

Any supplementations known to have a potential impact on prostate cancer or MGUS/ SMM are prohibited. All prior medications or supplements taken by the subject within 7 days before starting study are to be recorded. Patient should stop any food or supplement which has the potential to interact with curcumin or piperine, such as grapefruit prior to starting study treatment.

Curcumin and piperine can have an inhibitory effect on human cytochrome P450 isozymes and therefore have the potential to enhance the effect and interact with drugs metabolized by the P450 system (36,37,38). Curcumin and piperine appears to be most effect in inhibiting CYP3A both have potential inhibitory effects on other isozymes such as CYP1A2, and CYP2D6. One study has reported a potential negative impact on the activity of Tamoxifen (38). Caution should be used for patients on medications that are metabolized the cytochrome P450 system. A partial list of potential interactions is listed in Appendix 2 (37).

### 4.4 Duration of Follow-Up

For this pilot study, patient will continue on curcumin plus piperine supplementation and be followed for 52 weeks.

### 4.5 Drug Information

Curcumin C3 Complex® is an over-the-counter supplement manufactured by the Sabinsa Corporation, 20 Lake Drive East, Windsor, NJ 08520, USA. For this study, the Sabinsa will supply the curcumin and piperine combination in tablet form equivalent to the C3 complex. Each tablet will contain 1-gram curcumin and 5 mg piperine.

The supplement will be shipped in bulk from the Sabinsa Corporation to the Investigational Pharmacy where it will be stored at room temperature. Pharmacy will bottle a three-month supply of supplement for each patient, coinciding with each clinic visit. The supplement will be given to the patient at the time of each clinic visit by the study coordinator assigned to the study. Patients will be asked to return their empty bottles at each three-month visit. A pill count will be done by the study team to assess compliance.

## 5.0 STUDY PROCEDURES

### 5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining Informed Consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before Informed Consent was obtained.

All lab screening procedures must be performed within 30 days prior to registration, unless indicated otherwise (see study calendar).

**5.1.1 Informed Consent** (see Section 9.2)

**5.1.2 Demographics**

Demographic profile will include date of birth, gender, race, ethnicity and zip code.

**5.1.3 Review subject eligibility criteria**

Review of eligibility criteria as described in Section 3.0 to ensure subject qualification for study entry.

**5.1.4 Review previous and concomitant medications**

All prior medication taken by the subject within 7 days before starting the study is to be recorded in the medical record. At minimum, the start year of the medication should also be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 30 days after last study treatment. If a reportable adverse event (see Section 6.0) occurs within 30 days after last study treatment, recording of concomitant medications should continue until resolution of the adverse event.

### 5.1.5 Medical History

Complete medical, surgical and oncology history within 30 days of enrollment are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

### 5.1.6 Adverse Event Assessment

Baseline assessment of subject status will be conducted for determining future adverse events. See Section 6.0 for Adverse Event monitoring and reporting.

## 5.2 Removal of Subjects from Study Treatment and Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

**5.2.1** Subject voluntarily withdraws from treatment (follow-up permitted);

**5.2.2** Subject withdraws consent (termination of treatment and follow-up);

**5.2.3** Subject is unable to comply with protocol requirements;

**5.2.4** Subject experiences toxicity that makes continuation in the protocol unsafe;

**5.2.5** Treating physician judges that continuation on the study would not be in the subject's best interest;

**5.2.6** Lost to follow-up.

If a research subject cannot be located to document survival after 3 attempts by mail and/or telephone, the subject may be considered "lost to follow-up" All attempts to contact the subject must be documented.

**5.2.7** Patients who experience disease progression in which the standard of care would be to recommend alternative options (for example, radiation therapy or surgery for prostate cancer or chemotherapy for myeloma) will be removed from study. Patients with mild progression that would normally continue on active surveillance can continue on study.

# 6.0 ADVERSE EVENTS

Text below in italics is verbatim from "Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies", issued December 2012 by U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. The reporting requirements may be retrieved from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf?source=govdelivery.

## 6.1 Definitions

### 6.1.1 Adverse Event [21 CFR 312.32(a)]

*An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.*

*An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.*

This study will use the descriptions and grading scales from Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) for hematologic and non-hematologic toxicities. Detailed information may be found on the Cancer Therapy Evaluation Program (CTEP) website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Information for adverse events, whether reported by the subject, directly observed, or detected by physical examination, laboratory tests or other means, will be collected, recorded, followed and reported in the CRF as described in the following sections.

Severe adverse events experienced by subjects will be collected and reported from time of screening, throughout the study, and within 30 days of study intervention. Subjects who experience an ongoing adverse event related to a study procedure and/or study medication beyond 100 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the principal investigator. Study subjects will be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Medical conditions/diseases, or cancer related symptoms present before starting study treatment are considered adverse events only if they worsen after starting the study intervention. Adverse events occurring after the start of study treatment are to be recorded on the Adverse Events CRF.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy. In this case they will be recorded on the Adverse Events CRF.
As far as possible, each adverse event will also be described by:

- its duration (start and end dates),
- grading of severity,
- its relationship to the study intervention,
- the action(s) taken,
- outcome.

Events NOT meeting the Adverse Event Definition include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.
- Efficacy endpoints will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the disease under study.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be documented in the medical record.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**6.1.2** Suspected Adverse Reaction [21 CFR 312.32(a)]

*Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the study intervention (curcumin and piperine)caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the study intervention and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a study intervention.*

*Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the study intervention caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the study intervention actually caused the adverse event.*

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from study intervention administration: The event should occur after the study intervention is administered. The length of time from study intervention administration to event will be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge): Subject's response after study intervention discontinuation (de-challenge) will be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs/interventions the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Unrelated - The AE is clearly **NOT** related to the study treatment.
- Unlikely - The AE is **doubtfully related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Probable – The AE is **likely related** to the study treatment.
- Definite – The AE is **clearly related** to the study treatment.

**6.1.3** Unexpected [21 CFR 312.32(a)]

*An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.*

**6.1.4** Serious [21 CFR 312.32(a)]

*An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

**6.1.5** Life-threatening

*An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.*

## 6.2 Reporting Requirements for Serious Adverse Events

**6.2.1** Submitting Serious Adverse Events Reports to IRB

For serious adverse events, we will follow local IRB policies and procedures.

**6.2.2** Study Investigator Notification of Serious Adverse Events

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the Informed Consent must be reported to the study principal investigator within 24 hours of becoming aware of the event:

PI Name: Brea Lipe
Office Phone: 585-275-5863

**6.2.3** DSMC Notification of SAEs

All **expected** and **unexpected** adverse events and serious adverse events occurring after the subject has signed the Informed Consent and has started protocol treatment must be fully recorded in the subject's case record form.

All unexpected AND related SAEs should be reported to the DSMC Safety Coordinator within 5 calendar days of learning of the event, while other SAEs should be reported monthly to the DSMC. SAE reports are expected to include sufficient detail so that the WCI DSMC can determine the event, severity, toxicity grade, expectedness, relatedness, and treatment. The report should be updated to document resolution or any sequelae. The PI will report an aggregate listing of all AEs and SAEs for review at scheduled DSMC

meetings. The committee will review these reports and determine if further action is required.

SAEs that are determined to be related to study intervention AND unexpected require expedited reporting to the DSMC Safety Coordinator in addition to notification of the study PI by email.

DSMC Safety Coordinator: Erin M. Cebula, MPH, CCRP
Email: WCICTO_Qualilty@urmc.rochester.edu
For expedited SAEs (serious AND related AND unexpected), also copy Erin_Cebula@urmc.rochester.edu

The PI will report these events to the WCI DSMC in addition to sending a formal notification describing the event to all investigators. IRB will be notified of the event according to local regulations.

### 6.2.4 Summary of Expedited Serious Adverse Event Reporting

| | **Relationship to study investigational therapy** | **WCI Clinical Trials DSMC** | **IRB** | **PI** |
|---|---|---|---|---|
| Unexpected SAE | Related | 5 calendar days | 5 calendar days | 24 hrs |
| Unexpected SAE | Not-related | Monthly | Not reportable | 24 hrs |
| Expected SAE | Related | Monthly | Not reportable | 24 hrs |
| Expected SAE | Not-related | Monthly | Not reportable | 24 hrs |

## 7.0 STUDY CALENDAR

**Prostate Cancer Cohort:**

| Study Visits***** | Baseline**** | Day 30 | 12 weeks | 24 weeks | 36 weeks | 48 weeks | End of Study visit at 52 weeks. |
|---|---|---|---|---|---|---|---|
| H&P | X | X | X | X | X | X | X |
| AE assessment | | X | X | X | X | X | X |
| CBC/CMP | X | | X | X | X | X | X |
| PSA | X | | X | X | X | X | |
| PTT/INR | X | | | | | | |
| MpMRI* | X | | | | | X | |
| MIC-1&Banking (urine/serum)** | X | | X | X | | X | |
| Piperine*** | | Twice daily | | | | | |
| Curcumin*** | | Twice daily | | | | | |

*As per standard of care, MpMRI within six months prior to enrollment and at the completion of the study is encouraged but optional and not a requirement for study.
**15 ml of serum and urine samples will be collected for MIC-1 analysis and banking (see section 8.2).
***To be taken twice daily for 52 weeks.
****To be completed within 28 days  before starting treatment.
*****Study visits to be completed within seven day prior or seven days following the scheduled time.

**MGUS/Smoldering Myeloma Cohort:**

| Study Visits****** | Baseline***** | Day 30 | 12 weeks | 24 weeks | 36 weeks | 48 weeks | End of Study visit at 52 weeks. |
|---|---|---|---|---|---|---|---|
| H&P | X | X | X | X | X | X | X |
| AE Assessment | | X | X | X | X | X | X |
| Monoclonal Protein | X | | X | X | X | X | |
| Serum free light chains | X | | X | X | X | X | |
| PTT/INR | X | | | | | | |
| CBC/CMP | X | | X | | | | |
| MIC-1 (urine/serum)* | X | | X | X | | X | |
| PET/CT Scan, whole body MRI, or MRI of spine and pelvis** | X | | | | | | |
| Bone Marrow Biopsy*** | X | | | | | | |
| Piperine**** | | Twice daily | | | | | |
| Curcumin**** | | Twice daily | | | | | |

* 15 ml of serum and urine to be collected for MIC-1 and banking(see Section 8.2).
**For patients with low-risk SMM only (must be done within 12 months) per standard of care.
*** For patients with MGUS or low-risk SMM (must be done within 6 months) per standard of care.
**** To be taken twice daily for 52 weeks.
*****To be done within 28 days of starting treatment.
******Study Visits should be done within seven days prior or seven days following the scheduled time.

## 8.0 Correlative Studies

### 8.1 Assay Methodology

Enzyme-linked immunosorbent assay (ELISA) will be used to measure MIC-1 in plasma/serum/urine samples from enrolled subjects.

### 8.2 Specimen Banking

A total of 15 ml of urine and serum will be collected at each specified time point and processed as below. One ml of urine/serum is needed for each MIC-1 test. The remaining sample will be stored for potential future investigator of other potential biomarkers. Subject samples collected for this study will be stored in the laboratory of Brea Lipe. Specimens will be stored indefinitely or until they are used up. Samples from this study could be used by other investigators at URMC for IRB approved research purposes if approved by the PI.

MIC-1 testing will be done in the laboratory of Dev Karan, PhD who is located at the University of Wisconsin, Milwaukee. 1-2 ml of de-identified of blood and urine from each collection time point will be sent to his laboratory for testing. No data will be shared and all data analysis will be done at the University of Rochester.

With the subject's permission, any leftover specimens will be stored in the laboratory of Brea Lipe and used for future research studies by the CTO at WCI. These optional specimens will also be stored indefinitely or until they are used up. If the optional leftover specimen samples for storage and future use is denied or withdrawn by the subject (submitted in writing to the investigator), best efforts will be made to stop any additional studies and to destroy the specimens.

Peripheral blood processing:
1. 15 mL of Whole blood will be collected in 2 green top tubes
2. Centrifuge at 1800xg for 30 minutes in a swing bucket centrifuge (not a fixed angle) within 24 hours of collection
3. 15mL of Whole blood will be collected in 2 red top tubes
4. Blood will be allowed to clot prior to centrifugation at 4000 x g for 10 minutes
5. Blood will be stored at -80 degrees centigrade until analysis

Urine processing:
Urine will be stored at -80 degrees centigrade until analysis

## 9.0 DATA AND SAFETY MONITORING

### 9.1 Oversight and Monitoring Plan

Study Investigators will conduct continuous review of data and patient safety. The Principal Investigator (PI) will submit semi-annual progress reports of these data to the Data Safety Monitoring Committee for review. The review will include the number of patients enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, deviations, and responses observed. The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The PI will submit a copy of the AE spreadsheet along with a Progress Report and deviation log to the Data Safety Monitoring Committee (DSMC) at WCI for review. Actual review dates will be assigned when the study is activated.

The DSMC at the Wilmot Cancer Institute of the University of Rochester provides oversight of study progress and safety by review of accrual and adverse events at monthly meetings or more often if concerns arise. Any adverse event requiring expedited review per protocol will be submitted to the Safety Coordinator of the DSMC at WCI for determination as to whether further action is required. When patient safety is of concern, an interim meeting may be called in any of the following situations:

- Any serious adverse event that is serious, related AND unexpected must be reported within 5 calendar days to both the WCI DSMC Safety Coordinator and the local IRB (see institutional IRB guidelines). The WCI DSMC Chair will determine whether further action is required, and when patient safety is of concern.

- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the WCI DSMC for review at the quarterly meeting. SAE reports are expected to include sufficient detail so that the WCI DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Serious adverse events that require detailed reports (but not necessarily expedited) are non-hematologic toxicities of grades 3, 4 or 5, unless otherwise defined in the protocol.

The Safety Coordinator administratively coordinates reports and data collection and prepares documents for the WCI DSMC Chair and committee review. The Safety Coordinator will administratively monitor adverse event rates utilizing the report from the study database. If any study has had two or more of the same SAE's reported in a month or more than six of the same SAE's in six months, the WCI DSMC will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

**Stopping Rules:** The study activities will be monitored by the Data and Safety Monitoring committee (DSMC) at WCI. Also, SAE and suspected but unexpected SAE will be reported to the FDA according to FDA guidance (2012) and 21 CFR312.32.

The safety population is the total enrolled population (not stratified by disease cohort). We aim to terminate the study if there is evidence of unacceptably high rates of grade 3 or higher adverse events (AEs). A grade 3-5 AE rate of 20% or less would be considered acceptable (null hypothesis). A sequential Pocock-type boundary for repeated testing (35) was generated to continually monitor the grade 3-5 AE rate. The accrual will be halted if excessive numbers of grade 3-5 AEs are seen. Specifically, if the number of grade 3-5 AEs is equal to or exceeds $B_n$ out of n enrolled patients in Table 1, the trial will stop. The probability of crossing the boundary is at most 5% when the grade 3-5 AE rate is equal to the null rate of 20%. However, when the grade 3-5 AE rate is higher than the acceptable rate, the probability of early stopping increases. The probability of early stopping when the grade 3-5 AE rate is 40% is 79.8% with an expected sample size of 22.2 subjects.

Table 1: Early stopping rule boundaries for grade 3-5 adverse events

| Subjects experiencing grade 3-5 AE ($B_n$) | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subjects enrolled (n) | 3 | 4-5 | 6-8 | 9-11 | 12-14 | 15-17 | 18-21 | 22-24 | 25-27 | 28-31 | 32-35 | 36-38 | 39-40 |

## 10.0 REGULATORY CONSIDERATIONS

### 10.1 Protocol Review and Amendments

This protocol, the proposed Informed Consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the local IRB prior to implementation. Any changes in study conduct must be reported to each IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators. All decisions of the IRB concerning the conduct of the study must be made in writing.

### 10.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

### 10.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. ICH Consolidated Good Clinical Practice: Guidelines (E6) www.fda.gov/cder/guidance/iche6.htm
2. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
   - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
   - Title 21 Part 50 – Protection of Human Patients www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
   - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
   - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
   - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
3. State laws
4. Institutional research policies and procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the RSRB according to the local reporting policy.

## 11.0 REGISTRATION PROCEDURES

### 11.1 General Guidelines for URMC

Eligible subjects will be registered through the WCI Clinical Trials Office central registration process via OnCore. Registration must occur prior to the initiation of therapy. Any subject not registered to the protocol before treatment begins will be considered ineligible and registration will be denied. Subjects should be registered within 5 working days prior to starting treatment.

The completed source documentation provided for eligibility verification and registration must be kept in the subject binder for monitoring purposes and documentation of subject eligibility.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy following registration, the study team will be notified so that the subject's status can be changed in OnCore.

### 11.2 Registration Process

All ethical, regulatory, technical, and scientific approvals must be in place before study registrations will be accepted from a site.

All subjects will be registered centrally through the coordinating site Clinical Trials Office (CTO) which is located at the:

*James P. Wilmot Cancer Institute*
*University of Rochester Medical Center*
*Rochester, NY 14642*

The CTO at WCI will assist with the creation of a study-specific REDCap database at the University of Rochester. The PI and study statistician will determine the data points necessary to assess the study endpoint(s). Extraneous data will not be captured in the database. It is the expectation that all data has source documentation available. CTO personnel will be responsible for entering their patient data regularly into this database.

At the time of registration, the signed informed consent form and documents that support eligibility will be shared with the Genitourinary Team.

Any question regarding eligibility or that may arise during the conduct of the study should be addressed to:

Name: Brea Lipe, MD
Email: brea_lipe@urmc.rochester.edu
Phone: 585-275-5863

## 12.0 STUDY MANAGEMENT

### 12.1 Overall Study Organization

For this study, the WCI CTO is considered the Sponsor and a participating site for study activities.

### 12.2 Investigator Files and Retention of Documents

The study PI must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, subject diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

### 12.3 Case Report Forms

Case report forms (CRFs) will be completed for each subject enrolled. All CRFs will be complete and accurate. The medical chart and any other clinical worksheets, procedural reports, etc. are the source of verification of the data captured into the study database by each participating institution.

### 12.4 Study Monitoring

The study will be monitored by the WCI CTO according to the WCI DSMP to assure compliance to GCP and to assess the data quality and study integrity.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitors provided by WCI CTO will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data. Also, unexpected suspected SAEs will be reported to the FDA according to FDA guidance (2012) and 21 CFR312.32. Any death should be evaluated in the context of the natural history of the disease to determine the relationship to the study intervention.

## 13.0 STATISTICAL CONSIDERATIONS

### 13.1 Study Design Study Design

We aim to enroll 40 subjects total over 1 year. We will enroll 20 prostate cancer patients, 10 MGUS patients and 10 SMM patients. 50% of each cohort enrolled will be African American (10 African American prostate cancer patients, 5 African American MGUS patients and 5 African American SMM patients).

Sample size justification: We aim to estimate the response rate within each cohort. The sample size drives the precision of the estimate via the width of the associated confidence interval. We will provide 95% exact binomial two-sided confidence intervals for response rate. Table 1 provides the width of such intervals under a variety of possible response rates for N=20 (prostate cancer cohort) and N=10 (MGUS and SMM cohorts).

Table 1: Widths (and limits) of 95% exact binomial two-sided confidence intervals for a range of possible response rates.

| Response rate | N=20 | N=10 |
|---|---|---|
| 0.1 | 0.31 (0.01, 0.32) | 0.44 (0.003, 0.45) |
| 0.2 | 0.38 (0.06, 0.44) | 0.53 (0.03, 0.56) |
| 0.3 | 0.42 (0.12, 0.54) | 0.59 (0.07, 0.65) |
| 0.4 | 0.45 (0.19, 0.64) | 0.62 (0.12, 0.74) |
| 0.5 | 0.46 (0.27, 0.73) | 0.63 (0.19, 0.81) |
| 0.6 | 0.45 (0.36, 0.81) | 0.62 (0.26, 0.88) |
| 0.7 | 0.42 (0.46, 0.88) | 0.59 (0.35, 0.93) |
| 0.8 | 0.38 (0.56, 0.94) | 0.53 (0.44, 0.98) |
| 0.9 | 0.31 (0.68, 0.99) | 0.44 (0.56, 0.997) |

### 13.2 Study Endpoints

Primary Endpoint: Response rate after 12 months of curcumin plus piperine supplementation. Details on definition of response rate for each cohort are in Section 2.3. A response rate of at least 20% would be considered worthy of pursuing in future studies.

Secondary Endpoints:
-Progression rate after 12 months of curcumin plus piperine supplementation.
-Time to progression and/or death from initiation of curcumin plus piperine supplementation.
-Adverse event rates, summarized by grade and event type

Exploratory endpoints: MIC-1 levels in serum and urine samples.

### 13.3 Data Analysis Plan

We aim to estimate the response rate within disease cohort. The response rate will be defined as the number of subjects who experience a response over the total number of subjects in that disease cohort. Rates will be presented with associated 95% exact binomial two-sided confidence intervals. Rates of disease progression will be similarly described. We do not expect any deaths or loss to follow-up within 1 year so expect complete data for response assessment.

Progression-free survival within disease cohort will be graphically summarized via the Kaplan-Meier method. Progression-free survival will be defined as time from initiation of curcumin/piperine to disease progression or death, whichever occurs first. Subjects who do not die or progress will be censored at the end of follow-up.

Adverse events will be tabulated by grade and event type. The safety population will be the entire study population, not stratified by disease cohort. Subject-level AE rates will be calculated as the number of subjects experiencing the event of interest over the total number of subjects enrolled. Rates will be presented with associated 95% exact binomial confidence intervals.

MIC-1 will be summarized at each time point using descriptive statistics such as means and standard deviations, or medians and interquartile ranges. These will be plotted over time, within disease cohort, to provide a graphical summary of MIC-1 response to curcumin/piperine. We will use paired t-tests to compare within-subject MIC-1 changes (transforming MIC-1 if necessary to satisfy normality assumptions). We will compare MIC-1, and changes in MIC-1, between subjects who experience a response and those who do not experience a response using t-tests (after appropriate transformation, if needed). We will also assess the correlation of MIC-1 and SPEP/FLC in the MGUS/SMM cohort, and MIC-1 and PSA in the prostate cancer cohort. All MIC-1 analyses are considered exploratory and hypothesis-generating, as there is not adequate power for any definitive tests in this study.

We will stratify all descriptive analyses above by race as additional exploratory analyses. We acknowledge the small sample sizes in doing so, and thus no statistical testing involving race will be performed. These analyses will be considered exploratory and hypothesis generating.

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**Appendix 1: IMWG Response Criteria:** Adapted from Durie BGM, et al. Leukemia 2006.

| Response | IMWG criteria |
|---|---|
| sCR | CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4] |
| CR | Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3] |
| VGPR | Serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h |
| PR | > 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h<br><br>If the serum and urine M-protein are unmeasurable,[5] a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria<br><br>If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30%<br><br>In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required |
| MR | NA |
| No change/Stable disease | Not meeting criteria for CR, VGPR, PR, or progressive disease |
| Plateau | NA |

**MGUS/ SMM risk stratification:**

| Classification | Associated lab values |
|---|---|
| Low-risk MGUS | No risk factors present* |
| Low-Intermediate risk MGUS | 1 risk factor present* |
| High-Intermediate risk MGUS | 2 risk factors present* |
| High-risk MGUS | 3 risk factors present* |
| Low-risk SMM | Diagnosis of SMM and either m-protein ≥ 3g/dL, ≥10% plasma cells in marrow, or an abnormal FLC ratio |

*Risk factors include: serum monoclonal protein > 1.5 g/dL (15g/L), IgA or IgM protein type, abnormal FLC ratio). Rajkumar SV, et al. *Blood*. 2015;125(20):3069-3075.

Appendix 2: Common Substrates of Different CYP isozymes

**Table 2** Typical substrates of basic CYP isozymes

| CYP isozyme | Substrates |
|---|---|
| CYP1A2 | Clozapine, caffeine, paracetamol, theophylline, phenacetin, R-warfarin |
| CYP2C9 | Hexobarbital, zidovudine, losartan, paracetamol, testosterone, tolbutamide, phenytoin, celecoxib, S-warfarin |
| CYP2C19 | Hexobarbital, diazepam, zidovudine, omeprazole, pantoprazole, testosterone, phenytoin, R-warfarin, S-warfarin |
| CYP2D6 | Haloperidol, dextromethorphan, codeine, metoprolol, nortriptyline, paracetamol, pravastatin, propafenone |
| CYP3A4 | Alprazolam, atorvastatin, vincristine, halothane, hydrocortisone, zidovudine, carbamazepine, codeine, cortisol, caffeine, lidocaine, lovastatin, midazolam, nifedipine, paracetamol, tacrolimus, tamoxifen, testosterone, phenytoin, cyclosporine, cyclophosphamide, erythromycin, R-warfarin, S-warfarin |

**Note:** Data from Wadelius et al[57] and Kasichayanula et al.[5]
**Abbreviation:** CYP, cytochrome.

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| 03 Jan 2025 | 07:42 EST | Perrone, Benjamin | Signed this Document |
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| 24 Dec 2024 | 12:59 EST | Bates, Janna | Viewed the Document |
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| 23 Dec 2024 | 16:31 EST | Gallina, Audrey | Signed this Document |
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| 23 Dec 2024 | 15:17 EST | Awuah, Eunice | Viewed the Document |
| 23 Dec 2024 | 15:16 EST | Awuah, Eunice | Viewed the Document |
| 23 Dec 2024 | 15:03 EST | Awuah, Eunice | Viewed the Document |
| 23 Dec 2024 | 15:03 EST | Awuah, Eunice | Viewed the Document |
| 19 Dec 2024 | 11:05 EST | Torres, Jessica | Viewed the Document |
| 17 Dec 2024 | 09:13 EST | Zahn, Tracey | Viewed the Document |
| 16 Dec 2024 | 10:45 EST | Awuah, Eunice | Viewed the Document |
| 05 Dec 2024 | 15:41 EST | Awuah, Eunice | Downloaded the PDF |
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| 03 Dec 2024 | 12:03 EST | Applewhite, Ishmael | Downloaded the PDF |
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| Date | Time | Name | Action |
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| 20 Nov 2024 | 15:53 EST | Zhu, Allan | Viewed the Document |
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| 12 Nov 2024 | 15:28 EST | Zhu, Allan | Downloaded the PDF |
| 12 Nov 2024 | 15:27 EST | Zhu, Allan | Viewed the Document |
| 11 Nov 2024 | 17:02 EST | LeFeber, Chris | Viewed the Document |
| 08 Nov 2024 | 14:35 EST | Ali, Amar | Downloaded the PDF |
| 08 Nov 2024 | 14:35 EST | Ali, Amar | Viewed the Document |
| 07 Nov 2024 | 13:10 EST | Zhu, Allan | Viewed the Document |
| 06 Nov 2024 | 15:20 EST | Ali, Amar | Viewed the Document |
| 06 Nov 2024 | 14:25 EST | Zhu, Allan | Viewed the Document |
| 06 Nov 2024 | 10:22 EST | Zhu, Allan | Viewed the Document |
| 06 Nov 2024 | 09:56 EST | Poquadeck, Matt | Downloaded the PDF |
| 06 Nov 2024 | 08:11 EST | Torres, Jessica | Viewed the Document |
| 05 Nov 2024 | 08:36 EST | Grose, Valerie | Viewed the Document |
| 04 Nov 2024 | 12:21 EST | Zahn, Tracey | Viewed the Document |
| 04 Nov 2024 | 09:56 EST | Zhu, Allan | Viewed the Document |
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| 01 Nov 2024 | 10:10 EDT | Zahn, Tracey | Viewed the Document |
| 01 Nov 2024 | 09:02 EDT | Xu, Carina (Qinrui) | Viewed the Document |
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| 31 Oct 2024 | 16:22 EDT | Zhu, Allan | Viewed the Document |
| 31 Oct 2024 | 10:44 EDT | Zhu, Allan | Viewed the Document |
| 25 Oct 2024 | 13:33 EDT | Bates, Janna | Viewed the Document |
| 24 Oct 2024 | 15:25 EDT | Bates, Janna | Viewed the Document |
| 24 Oct 2024 | 11:35 EDT | Bates, Janna | Viewed the Document |
| 24 Oct 2024 | 10:43 EDT | Ali, Amar | Viewed the Document |
| 24 Oct 2024 | 10:38 EDT | Zhu, Allan | Viewed the Document |
| 24 Oct 2024 | 10:34 EDT | Zahn, Tracey | Viewed the Document |
| 23 Oct 2024 | 15:54 EDT | Ali, Amar | Viewed the Document |
| 23 Oct 2024 | 13:21 EDT | Torres, Jessica | Viewed the Document |
| 15 Oct 2024 | 13:52 EDT | Ali, Amar | Viewed the Document |
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| Date | Time | Name | Action |
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| 19 Sep 2024 | 11:53 EDT | Snyder, Joy | Viewed the Document |
| 17 Sep 2024 | 12:14 EDT | Devendorf, Rachel | Viewed the Document |
| 10 Sep 2024 | 11:12 EDT | Applewhite, Ishmael | Downloaded the PDF |
| 10 Sep 2024 | 11:12 EDT | Applewhite, Ishmael | Downloaded the PDF |
| 10 Sep 2024 | 11:11 EDT | Applewhite, Ishmael | Downloaded the PDF |
| 10 Sep 2024 | 11:11 EDT | Alshlah, Ali | Viewed the Document |
| 10 Sep 2024 | 11:11 EDT | Applewhite, Ishmael | Viewed the Document |
| 10 Sep 2024 | 11:11 EDT | Alshlah, Ali | Viewed the Document |
| 28 Aug 2024 | 14:25 EDT | Torres, Jessica | Downloaded the PDF |
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| 15 Aug 2024 | 13:50 EDT | Awuah, Eunice | Viewed the Document |
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| 07 Aug 2024 | 14:11 EDT | Shriver, Jennifer | Signed this Document |
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| 07 Aug 2024 | 14:10 EDT | Shriver, Jennifer | Viewed the Document |
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| 22 Jul 2024 | 08:07 EDT | Malta, Taylor | Signed this Document |
| 22 Jul 2024 | 08:07 EDT | Malta, Taylor | Viewed the Document |
| 17 Jul 2024 | 11:34 EDT | Awuah, Eunice | Viewed the Document |
| 10 Jul 2024 | 17:06 EDT | Lipe, Brea | Viewed the Document |
| 20 Jun 2024 | 10:25 EDT | Zahn, Tracey | Viewed the Document |
| 20 Jun 2024 | 10:15 EDT | Torres, Jessica | Viewed the Document |
| 06 Jun 2024 | 15:58 EDT | Bates, Janna | Viewed the Document |
| 06 Jun 2024 | 15:57 EDT | Diaz, Ashley | Viewed the Document |
| 06 Jun 2024 | 15:16 EDT | Torres, Jessica | Viewed the Document |
| 14 May 2024 | 10:02 EDT | Torres, Jessica | Viewed the Document |

| Date | Time | Name | Action |
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| 18 Apr 2024 | 07:20 EDT | Zahn, Tracey | Viewed the Document |
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| 26 Mar 2024 | 10:35 EDT | LeFeber, Chris | Viewed the Document |
| 25 Mar 2024 | 11:53 EDT | Zahn, Tracey | Signed this Document |
| 25 Mar 2024 | 11:48 EDT | Zahn, Tracey | Viewed the Document |
| 20 Mar 2024 | 10:38 EDT | Crouch, Marina | Viewed the Document |
| 20 Mar 2024 | 10:37 EDT | Crouch, Marina | Viewed the Document |
| 14 Mar 2024 | 09:37 EDT | Fisher, Stuart | Viewed the Document |
| 13 Mar 2024 | 13:31 EDT | Grose, Valerie | Viewed the Document |
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| 12 Mar 2024 | 14:56 EDT | Lin, Amy | Viewed the Document |
| 12 Mar 2024 | 11:13 EDT | Fisher, Stuart | Viewed the Document |
| 11 Mar 2024 | 12:49 EDT | French, Krista | Viewed the Document |
| 07 Mar 2024 | 15:36 EST | Burrows, Kaitlyn | Viewed the Document |
| 07 Mar 2024 | 08:33 EST | Johnston, Melanie | Viewed the Document |
| 06 Mar 2024 | 09:16 EST | Burrows, Kaitlyn | Viewed the Document |
| 04 Mar 2024 | 07:40 EST | Torres, Jessica | Viewed the Document |
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| 29 Feb 2024 | 09:44 EST | Ravikumar, Pavithra | Signed this Document |
| 29 Feb 2024 | 09:42 EST | Ravikumar, Pavithra | Viewed the Document |
| 29 Feb 2024 | 09:21 EST | Diaz, Ashley | Viewed the Document |
| 28 Feb 2024 | 09:41 EST | Fisher, Stuart | Viewed the Document |
| 27 Feb 2024 | 13:56 EST | Lipof, Jodi | Viewed the Document |
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| 26 Feb 2024 | 11:09 EST | Grose, Valerie | Viewed the Document |
| 26 Feb 2024 | 11:00 EST | Fisher, Stuart | Viewed the Document |
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| 23 Feb 2024 | 14:28 EST | Torres, Jessica | Downloaded the PDF |
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| 23 Feb 2024 | 08:02 EST | Grose, Valerie | Viewed the Document |
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| Date | Time | Name | Action |
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| 22 Feb 2024 | 09:49 EST | Fisher, Stuart | Viewed the Document |
| 16 Feb 2024 | 07:24 EST | Littleton, Jamie | Signed this Document |
| 16 Feb 2024 | 07:23 EST | Littleton, Jamie | Viewed the Document |
| 16 Feb 2024 | 07:23 EST | Littleton, Jamie | Viewed the Document |
| 15 Feb 2024 | 12:16 EST | Torres, Jessica | Viewed the Document |
| 13 Feb 2024 | 10:28 EST | Littleton, Jamie | Viewed the Document |
| 13 Feb 2024 | 10:22 EST | Littleton, Jamie | Viewed the Document |
| 13 Feb 2024 | 10:18 EST | Littleton, Jamie | Viewed the Document |
| 09 Feb 2024 | 09:33 EST | Torres, Jessica | Viewed the Document |
| 07 Feb 2024 | 10:04 EST | Torres, Jessica | Viewed the Document |
| 01 Feb 2024 | 17:22 EST | French, Krista | Viewed the Document |
| 29 Jan 2024 | 12:49 EST | Fisher, Stuart | Viewed the Document |
| 26 Jan 2024 | 12:57 EST | Diaz, Ashley | Viewed the Document |
| 22 Jan 2024 | 11:46 EST | Forrett, Noel | Signed this Document |
| 22 Jan 2024 | 11:40 EST | Forrett, Noel | Viewed the Document |
| 22 Jan 2024 | 08:36 EST | Torres, Jessica | Viewed the Document |
| 19 Jan 2024 | 14:45 EST | Diaz, Ashley | Viewed the Document |
| 19 Jan 2024 | 09:22 EST | Bates, Janna | Viewed the Document |
| 18 Jan 2024 | 11:39 EST | French, Krista | Viewed the Document |
| 18 Jan 2024 | 09:01 EST | Devendorf, Rachel | Downloaded the PDF |
| 17 Jan 2024 | 14:15 EST | Myrick, Tracey | Viewed the Document |
| 17 Jan 2024 | 13:18 EST | Devendorf, Rachel | Viewed the Document |
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| 16 Jan 2024 | 14:19 EST | French, Krista | Signed this Document |
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| 11 Jan 2024 | 15:27 EST | Nguyen, Lisa | Signed this Document |
| 11 Jan 2024 | 15:27 EST | Nguyen, Lisa | Viewed the Document |
| 11 Jan 2024 | 15:25 EST | Earle, Victoria | Signed this Document |
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| 10 Jan 2024 | 10:05 EST | Fisher, Stuart | Viewed the Document |
| 09 Jan 2024 | 10:56 EST | Richards, Kyle | Signed this Document |
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| 02 Jan 2024 | 16:21 EST | Earle, Victoria | Viewed the Document |

| Date | Time | Name | Action |
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| 01 Jan 2024 | 23:18 EST | Victor, Adrienne | Signed this Document |
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| 29 Dec 2023 | 15:07 EST | Diaz, Ashley | Viewed the Document |
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| 29 Dec 2023 | 08:53 EST | Baron, Samuel | Signed this Document |
| 29 Dec 2023 | 08:52 EST | Baron, Samuel | Viewed the Document |
| 28 Dec 2023 | 08:00 EST | Houwers, Lisa | Signed this Document |
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| 26 Dec 2023 | 16:33 EST | Dougherty (Almeter), Angela | Signed this Document |
| 26 Dec 2023 | 16:33 EST | Dougherty (Almeter), Angela | Viewed the Document |
| 26 Dec 2023 | 16:08 EST | Earle, Victoria | Downloaded the PDF |
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| 26 Dec 2023 | 12:27 EST | Burrows, Kaitlyn | Viewed the Document |
| 26 Dec 2023 | 12:24 EST | Burrows, Kaitlyn | Viewed the Document |
| 26 Dec 2023 | 11:54 EST | Le, Jim | Signed this Document |
| 26 Dec 2023 | 11:54 EST | Le, Jim | Viewed the Document |
| 20 Dec 2023 | 08:59 EST | Grose, Valerie | Signed this Document |
| 20 Dec 2023 | 08:59 EST | Grose, Valerie | Viewed the Document |
| 20 Dec 2023 | 08:39 EST | Houwers, Lisa | Viewed the Document |
| 19 Dec 2023 | 19:04 EST | Sievert, Lynn | Signed this Document |
| 19 Dec 2023 | 19:03 EST | Sievert, Lynn | Viewed the Document |
| 19 Dec 2023 | 10:06 EST | LeFeber, Chris | Signed this Document |
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| 19 Dec 2023 | 09:19 EST | Joseph, Jean | Signed this Document |
| 19 Dec 2023 | 09:19 EST | Joseph, Jean | Viewed the Document |
| 19 Dec 2023 | 08:21 EST | Zhu, Allan | Signed this Document |
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| 18 Dec 2023 | 17:14 EST | Guercio, Brendan | Signed this Document |
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| 18 Dec 2023 | 14:50 EST | Littleton, Jamie | Downloaded the PDF |
| 18 Dec 2023 | 12:14 EST | Geiser, Tom | Signed this Document |
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| Date | Time | Name | Action |
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| 18 Dec 2023 | 12:01 EST | Geiser, Tom | Viewed the Document |
| 18 Dec 2023 | 10:48 EST | Geiser, Tom | Viewed the Document |
| 18 Dec 2023 | 10:07 EST | Fisher, Stuart | Signed this Document |
| 18 Dec 2023 | 10:05 EST | Fisher, Stuart | Viewed the Document |
| 18 Dec 2023 | 09:48 EST | Burrows, Kaitlyn | Viewed the Document |
| 18 Dec 2023 | 09:44 EST | Peck, Helen | Downloaded the PDF |
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| 18 Dec 2023 | 08:50 EST | Littleton, Jamie | Downloaded the PDF |
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| 18 Dec 2023 | 08:43 EST | Traynor, Chad | Signed this Document |
| 18 Dec 2023 | 08:41 EST | Traynor, Chad | Viewed the Document |
| 18 Dec 2023 | 07:02 EST | Crouch, Marina | Viewed the Document |
| 18 Dec 2023 | 07:01 EST | Crouch, Marina | Viewed the Document |
| 18 Dec 2023 | 07:00 EST | Crouch, Marina | Viewed the Document |
| 14 Dec 2023 | 19:52 EST | Passero, Frank | Signed this Document |
| 14 Dec 2023 | 19:51 EST | Passero, Frank | Viewed the Document |
| 14 Dec 2023 | 14:50 EST | Fries, Gina | Signed this Document |
| 14 Dec 2023 | 14:50 EST | Fries, Gina | Viewed the Document |
| 14 Dec 2023 | 13:56 EST | Diaz, Ashley | Viewed the Document |
| 14 Dec 2023 | 13:10 EST | Diaz, Ashley | Viewed the Document |
| 14 Dec 2023 | 10:42 EST | Bailey (Deruchia), Renee | Signed this Document |
| 14 Dec 2023 | 10:41 EST | Bailey (Deruchia), Renee | Viewed the Document |
| 14 Dec 2023 | 10:30 EST | Poquadeck, Matt | Signed this Document |
| 14 Dec 2023 | 10:29 EST | Poquadeck, Matt | Viewed the Document |
| 14 Dec 2023 | 07:14 EST | Drawe, Zachary | Signed this Document |
| 14 Dec 2023 | 07:14 EST | Drawe, Zachary | Viewed the Document |
| 14 Dec 2023 | 07:12 EST | Drawe, Zachary | Viewed the Document |
| 13 Dec 2023 | 18:19 EST | Sahasrabudhe, Deepak | Signed this Document |
| 13 Dec 2023 | 18:19 EST | Sahasrabudhe, Deepak | Viewed the Document |
| 13 Dec 2023 | 15:38 EST | Charbonneau, Roger | Signed this Document |
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| 13 Dec 2023 | 15:16 EST | Diaz, Ashley | Signed this Document |
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| Date | Time | Name | Action |
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| 13 Dec 2023 | 14:30 EST | Lipe, Brea | Signed this Document |
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| 13 Dec 2023 | 10:29 EST | Alshlah, Ali | Signed this Document |
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| 13 Dec 2023 | 09:18 EST | Bates, Janna | Downloaded the PDF |
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| 12 Dec 2023 | 17:38 EST | Rashid, Hani | Signed this Document |
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| 12 Dec 2023 | 14:19 EST | Converse, Licia | Signed this Document |
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| 12 Dec 2023 | 14:10 EST | Zinchenko, Erica | Signed this Document |
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| 12 Dec 2023 | 13:35 EST | Li, Na | Signed this Document |
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| 12 Dec 2023 | 13:00 EST | Weisbrod, Dennis | Signed this Document |
| 12 Dec 2023 | 13:00 EST | Weisbrod, Dennis | Viewed the Document |
| 12 Dec 2023 | 12:55 EST | Lee, Benjamin | Signed this Document |
| 12 Dec 2023 | 12:55 EST | Lee, Benjamin | Viewed the Document |
| 12 Dec 2023 | 12:53 EST | Ali, Amar | Signed this Document |
| 12 Dec 2023 | 12:53 EST | Ali, Amar | Viewed the Document |
| 12 Dec 2023 | 12:46 EST | Sargent, Susan | Signed this Document |
| 12 Dec 2023 | 12:45 EST | Johnston, Melanie | Signed this Document |
| 12 Dec 2023 | 12:45 EST | Johnston, Melanie | Viewed the Document |
| 12 Dec 2023 | 12:44 EST | Sargent, Susan | Viewed the Document |
| 12 Dec 2023 | 12:42 EST | Torres, Jessica | Signed this Document |
| 12 Dec 2023 | 12:42 EST | Torres, Jessica | Viewed the Document |
| 12 Dec 2023 | 12:41 EST | Torres, Jessica | Viewed the Document |
| 12 Dec 2023 | 12:06 EST | Burrows, Kaitlyn | Signed this Document |
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| 12 Dec 2023 | 12:05 EST | Burrows, Kaitlyn | Viewed the Document |
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| Date | Time | Name | Action |
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| 12 Dec 2023 | 11:43 EST | Fung, Chunkit | Signed this Document |
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| 12 Dec 2023 | 11:42 EST | Fung, Chunkit | Viewed the Document |
| 12 Dec 2023 | 11:42 EST | Bates, Janna | Viewed the Document |
| 12 Dec 2023 | 11:34 EST | Devendorf, Rachel | Viewed the Document |
| 12 Dec 2023 | 11:34 EST | Cifelli, Janice | Signed this Document |
| 12 Dec 2023 | 11:34 EST | Cifelli, Janice | Viewed the Document |
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| 12 Dec 2023 | 11:34 EST | Frye, Thomas | Signed this Document |
| 12 Dec 2023 | 11:33 EST | Frye, Thomas | Viewed the Document |
| 12 Dec 2023 | 11:20 EST | Devendorf, Rachel | Assigned Document Type and Added Document Attributes<br>Type: Added<br>Document Type: Current Protocol<br>Type: Added<br>Version Date: 07 Dec 2023<br>Type: Added<br>Version Number: Version 14<br>Type: Added<br>URCC Number: UMLT20123<br>Type: Added<br>Sponsor Protocol Number: UMLT20123<br>Type: Added<br>Site: University of Rochester Wilmot Cancer Institute |
| 12 Dec 2023 | 11:01 EST | Devendorf, Rachel | Uploaded this Document |