PROTOCOL NUMBER: 2016-1051

PROTOCOL TITLE: **Methylene Blue for the Treatment of Intractable Pain Associated with Oral Mucositis.**

SHORT TITLE: MOM's PAIN (Methylene Blue for Oral Mucositis' PAIN)

Randomized controlled trial comparing 4 intervention arms, including 3 different concentrations of Methylene Blue oral rinse combined with conventional therapy and conventional therapy, in patients with intractable pain associated with oral mucositis.

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1.0 Background and Rationale

Oral mucositis is a debilitating sequela of treatment in the cancer patient, one that affects oral intake, hygiene, treatment and quality of life. Oral mucositis has been reported in 97% - 100% of patients with head and neck cancer receiving fractionated radiation therapy, in 80% of patients receiving chemotherapy for stem cell transplantation and 50% of patients receiving chemotherapy for lymphoma or solid tumors (1).

Mucositis is caused by damage to submucosal structures leading to endothelial cell damage resulting in abnormalities in mucosal epithelial growth. It is the product of a series of biological processes initiated by cellular damage (in the form of radiation and chemotherapy in the cancer population) causing the early release of an inflammatory cascade, which subsequently activates apoptosis. Clinically, patients manifest early with erythema and discoloration, leading to ulceration in latter stages with pain symptoms ranging from slight discomfort to allodynia preventing oral intake. In chemotherapy patients, symptoms first begin 3-5 days after initiation of treatment, with ulceration approximately two days later and resolution 2 weeks later. In radiation patients with mucositis, escalation of doses beyond 20Gy typically produce signs of mucositis (erythema) and progressively worsen to ulceration as dose increases beyond 30Gy (2). These ulcerations may last up to 4 weeks after completion of treatment (3).

In the cancer population, significant morbidity is associate with mucositis. Infection rates double in patients with mucositis during chemotherapy for solid tumors or lymphoma (4), and ulceration leading to systemic infection is a risk in these immunocompromised patients. A reduction of next dose chemotherapy is twice as common after cycles where patients had mucositis, as well as a 50% longer duration of hospitalization. The estimated cost for hospitalizations per chemotherapy cycle in patients with oral mucositis is $6,277, versus $3,893 without (5).

Mucositis decreases oral intake secondary to pain, hastening the need for supplemental nutrition via TPN or gastronomy tube and thus increases the risk of malnourishment and infection.

In light of the significant debility associated with mucositis, proper treatment is critical in the immunocompromised patient. Various oral preparations containing local anesthetics, anti-inflammatories, antimicrobials, antiseptics and mucosal coating agents have been investigated; however, insufficient evidence prevents most from being recommended and used regularly (6, 7).

Methylene blue (MB) has been described in the pain literature as an intradiscal injectate for discogenic low back pain (8), as a treatment of oral lichen planus (9) and as a diagnostic tool for oral cancer and precancerous lesions (10). A case series evaluated the intradermal injection of methylene blue for pruritis ani, and symptoms improved in 96% of the patients and resolved in 65% (11). It is postulated that by controlling neuroinflammation at the microglial level, methylene blue may be useful in diseases such as amyotrophic lateral sclerosis (12).

Anecdotal experience of the use of MB in patients with acute and chronic pain associated to oral mucositis has shown very positive outcomes regarding symptom control and decreasing the need for opiates in patients undergoing cancer therapy seen by our consulting service for intractable pain related to oral mucositis. The primary complaint of all patients has been oral pain compromising different structures including tongue and inner lips, sublingual and oral mucosa. The majority had expressed difficulty with feeding secondary to pain. They also had reported weight loss as a result of decreased oral intake. Multiple patients had been hospitalized for pain and failure to thrive, others had been seen as a requested consultations in the Emergency Department, and others had been outpatient clinic visits. They all had expressed suboptimal pain control despite systemic therapy with opiates. Patients had been instructed to take a mouth full of 0.025%, 0.05% or 0.1% MB diluted in normal saline. The mixture is to be kept in the painful site for five minutes then to gargle and spit. The same steps had been to be reeated every 6 hours. The majority of patients had experienced a sustained decrease of more than 50% in their pain scores at 3 weeks follow up. The morphine equivalent daily dose on those that apply significantly reduced or eliminated. The overall patient satisfaction has been very high and the treatment has been well-tolerated, with sustained analgesia. No alteration of taste or motor function reported; no sensory changes or anesthesia of the healthy mucosa has been found. About 80 patients have been treated with MB with concentrations of 0.025%, 0.05% or 0.1%, and we haven't observed any adverse event at any of concentrations.

We propose a randomized controlled trial comparing 4 intervention arms, including 3 concentrations of Methylene Blue (MB) oral rinse combined with conventional therapy and conventional therapy which includes mouth rinses with local anesthetics and cleaning solutions and systemic analgesics given orally or intravenously. In patients with intractable pain associated with oral mucositis defined as the presence of pain or oral dysfunction despite conventional therapy. To the best of our knowledge, no study of this kind has been performed.

2.0 Study Objective

The primary objective is to evaluate the efficacy of MB in reducing the severity of mucositis-related pain, measured by Numeric Rating Scale (NRS), in cancer patients who underwent or are undergoing chemotherapy or radiation therapy. Patients will be randomized to one of 4 intervention arms, including conventional therapy and conventional therapy plus MB with one of 3 concentrations (0.025%, 0.05% or 0.1%) oral rinse to swish and spit.

2.1 Primary Outcomes:

Oral mucositis pain reduction (measured by using the Numeric Rating Scale (NRS); from 0, representing no pain, to 10, representing the worst possible pain) from baseline to 7 days post treatment. The pain scale is included in the Modified Harris mucositis-related pain assessment tool.

2.2 Secondary Outcomes:

1. Oral functioning (eat, swallow, talk: unable=2, difficulty=1, able=0. Oral functioning score is the total score of 3 categories, ranged 0-6). Scale is included in the Modified Harris mucositis-related pain assessment tool. Measurements are obtained at day 0, 1, 2, and 7.

2. Presence of absence of pain and pain score measured by NRS at day 0, 1, 2, and 7.

3. Number of MB doses needed to achieve pain relief at 0, 1, and 2 days post MB administration

4. Morphine equivalent daily dose (MEDD) used for oral mucositis pain at 2, and 7 days post MB administration.

5. Incidence of untoward side effects immediately after MB administration and at 1, 2, 7 days post MB administration.

3.0 Background Drug Information

MB is a phenothiazine derivative administrated intravenously for the treatment of drug-induced methemoglobinemia, currently its only labeled use. It has also been used topically as a photosensitizer for photodynamic therapy in the treatment of mucocutaneous lesions such as herpes labialis and oral lichen planus. In the laboratory setting it is utilized as an indicator dye, and in cancer treatment, it is used for preoperative planning for breast cancer patients undergoing lymph node biopsy. Although the exact mechanism of action of MB has not been established, it is known to metabolize to a colorless form, leukomethylene blue, forming a reversible oxidation-reduction system, which explains its utility in methemoglobinemia. It is also known to be neurolytic when injected intradermally (11), and as a result of this observation, it has been used intradiscally for the treatment of discogenic pain (8) and into pelvic fracture sites for associated pain (13). These properties may help explain the anti-

inflammatory and analgesic effects of MB, leading to its proposed clinical utility in painful oral mucositis.

3.1 Dosages and Administration

For oral administration, no commercially available preparation exist, but it has been prepared by diluting MB 1%, 5-10 mL of commercially available 10mg/mL solution with 100-200 mL of water (9, 14). Based on our anecdotal experience, at MD Anderson same dilution has been used in more than 80 patients with pain associated to oral mucositis with no adverse events.

Patients be instructed to take one mouth full (6 – 10 mL of the solution to be held at the painful sites for five minutes then to swish and spit. The same steps to be repeated every 6 hours (the total mix of 100 mL will provide up to 6-10 uses).

3.2 Adverse Effects, Precautions, and Contraindications

If used systemically, MB administered intravenously (IV) or orally (PO) in large doses may cause nausea, vomiting, abdominal pain, dizziness, headache, profuse sweating, dyspnea, mental confusion, and irritation at the infusion site (only seen with IV). The most common side effects of oral administration are adverse gastrointestinal effects and dysuria. MB causes a blue-green discoloration to saliva, urine, feces, and skin. The skin stains may be removed by application of hypochlorite solution. MB is contraindicated in patients with known hypersensitivity to MB, women who are or may become pregnant (MB is a teratogen), patients with known or suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency, and those who are taking serotonergic drugs. It should be used cautiously in patients with severe renal impairment. Subcutaneous, intrathecal, and intraspinal route of administration should be avoided. Long-term use of MB is also associated with anemia. Therefore, monitoring of complete blood counts is advised (15). These adverse events have been studied in both large IV and PO administration and appear to be much more limited with oral administration (as above). In our study, the use of 100 mL equals 4 - 6 mouth full doses. It might expose patients to a dose of 2-6 mg of MB if swallowed, trans-mucosal absorption if any, when used in an oral rinse, is considered negligible. Formal toxicity monitoring may not be required. Therefore, formal toxicity monitoring will not be necessary. Safety data will be monitored by principle investigator.

If not available, a pregnancy test will be done in females in child-bearing condition (non-menopausal). This study requires women of child bearing potential to use contraception or abstinence from sex during the treatment period and for 30 days after their last dose. Urine pregnancy test will be obtained within 48 hours of staring the study.

3.3 Drug Interactions

MB is an inhibitor of monoamine oxidase (MAO), in full doses; serious central nervous system reactions (serotonin syndrome) have been reported with patients who are concurrently taking serotonin-modulating medications (16). Discontinuing the serotonergic medication prior to administration of MB can reduce the risk of serotonin syndrome. If given systemically, the Food and Drug Administration (FDA) recommends most serotonergic drugs to be discontinued for at least two weeks prior to MB treatment in non-emergency situations

(16). Most of the reported cases of serotonin syndrome occurred when MB was used as a diagnostic agent in the operative setting, in patients taking selective serotonin reuptake inhibitors (SSRI) or selective serotonin-norepinephrine reuptake inhibitors (SNRI). Other drug interactions are similar to those with other drugs having MAO-inhibiting properties, e.g., anticholinergics, alpha/beta-agonists, and tricyclic anti-depressants (15). These interactions have been studied in the IV route of administration and are likely more limited with oral administration of small dosages as proposed in this study.

3.4 Preparations, Stability, and Storage

MB is a thiazine dye that is soluble in water and forms a deep blue solution. It is available as a 1%, 10 mg/mL solution that should be stored at 20°C to 25°C (68°F to 77°F) but may be exposed to temperatures ranging from 15°C to 30°C (59°F to 86°F).

4.0 Study Design

This study is a prospective, randomized trial involving adult patients with intractable pain associated with oral mucositis. This study will have four intervention arms - MB 0.025 arm, MB 0.05 arm, MB 0.1 arm and a control arm. MB arm will receive one of 0.025%, 0.05% or 0.1% MB solution in addition to conventional therapy (0.025%, 0.05%, and 0.1% MB solution for MB 0.025, MB 0.05, and MB 0.1 arm, respectively), and the control arm will receive conventional therapy for 2 days, then will receive one of 3 solutions which will be randomly selected if they would like to receive MB solution.

5.0 Study Population

Patients will be randomized as described below. Neither the physician nor the patient will be involved in the randomization process. Physician, patient, study coordinator and data collectors will be blinded to the concentration of the medication used.

5.1 Sample Size

For the primary outcome (Oral mucositis pain reduction from baseline to 7 days after entering the study), we expect the mean pain reduction of 0, 2, 2.5, and 3 points for control, MB 0.025, MB 0.05, and MB 0.1 arms, respectively. In a one-way ANOVA study, sample sizes of 15, 15, 15, and 15 are obtained from the 4 arms whose means are to be compared. The total sample of 60 subjects achieves 83% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means is represented by their standard deviation which is 1.14 (means of 0, 2, 2.5, and 3 for control, MB 0.025, MB 0.05, and MB 0.1 arms, respectively). The common standard deviation within a group is assumed to be 2.5.

5.2 Inclusion Criteria

1. Patients with a cancer diagnosis, receiving chemotherapy, radiation therapy or the combination.
2. Patients with a current diagnosis of oral mucositis.
3. Patients with pain and oral dysfunction associated with oral mucositis despite conventional therapy.
4. Age greater than or equal to 18 years.
5. Voluntary written consent.
6. Patient must agree to use of contraception or abstinence from sex during the treatment period and for 30 days after patients' last dose of study MB.

5.3 Exclusion Criteria

1. Patients with known allergy to MB.
2. Patients taking medications with known significant drug interactions.
3. Pregnant or lactating patients.
4. Patients who are cognitively impaired and unable to consent for the study.
5. Patients with risk of Broncho-aspiration based on documented swallowing test by a Speech Pathologist (if available).
6. Patients with known history of G6PD deficiency.
7. Patients undergoing any other experimental intervention for oral mucositis.
8. Patients who have no pain or impairment in oral function, patients who are not symptomatic.
9. Patients with head and neck cancer.
10. Patients on serotonergic drugs.

5.4 Withdrawal Criteria

Patients can withdrawal from the study at any time. If the patient no longer wishes to participate, they will receive conventional care.

5.5 Conventional Therapy Criteria

The conventional therapy includes oral rinses and systemic therapy (oral, transdermal and intravenous analgesic. No response to conventional therapy means using other treatments and still symptomatic.

6.0 Methods

6.1 Patient enrollment and registration

Patients will be recruited for the study through multiple care sites at MD Anderson Cancer Center. Patients arriving at the MDACC Emergency Center with complaints consistent with mucositis will be screened for eligibility for enrollment in the study. Other patients treated at

the Pain Management Center as well as those referred for mucositis treatment from the Oncology medical wards for mucositis will also be screened.

6.2 Informed Consent

After patients are screened and found eligible for the study, they will be asked if they are interested in participating. If interested, patients will have the informed consent (IC) explained to them by a research team member. The study will use the electronic informed consent in EPIC to consent each participant, however, in the event that an electronic consent cannot be obtained, then the patient will sign, date, and put the time on the IC hard copy. The consenter will also sign, date and put time on the IC. A copy of the IC will be made and given to the patient for their records. The original copy will be sent to Health Information Management for storage and another copy will be locked in secure location by the principal investigator.

6.3 Patient randomization and assignment to treatment arm

The study will accrue up to 60 patients with a 1:1:1:1 ratio to include 4 intervention arms. Those include conventional therapy, conventional therapy + MB 0.025%, conventional therapy + MB 0.05%, and conventional therapy + MB 0.1%; each group will include 15 patients. We will conduct stratified randomization by baseline pain (baseline NRS 0-5 vs. 6-10) and oral functioning score (0-3 vs. 4-6). The primary endpoint is the reduction in pain score from baseline to 7 days. Patient randomization will be done through the Clinical Trial Conduct website. Study staff will be uninvolved in the randomization process.

Once a patient is enrolled in the study, the Investigational Pharmacy at MDACC retrieves the randomized treatment arm information from the Clinical Trial Conduct website. Once a patient is randomized to a treatment arm, Investigational Pharmacy will relay the information to the dispensing pharmacy at MDACC.

Study staff will contact patients either in person if as an inpatient or by phone at every follow-up the encounter to check for adverse events during routine patient encounters or via telephone calls.

Patients who were randomized to conventional arm will have an option to cross over to one of 3 MB arms, which they will be randomly allocated to, after completing 2 day pain measurements.

6.4 Administration of pharmacological agent

Preparation and randomization of the study medication (MB) for each patient will be performed by a compound research pharmacy. The study medication will be available to the patient through the dispensing pharmacy at MD Anderson Cancer Center. Patients will receive instructions on how to take study medications.

The participants will take MB via oral swish and spit technique or to continue conventional therapy. A small cup will be given to the patient to use to take the MB. There is no need for strict precision of the MB because patients' mouth size are variable, usually takes 6-10mL per rinse. Those on the MB arm will be instructed to take one mouth full (6 – 10 mL out of a total of 100 mL which might last 2-3 days only if used regularly) of the solution to be held at the painful sites for five minutes then to swish and spit. The same steps to be repeated every 6 hours (the total mix of 100 mL will provide up to 6-10 uses). If needed, patients will be given the solution to complete the treatment at home. Patients are instructed to use it every 6 hours until pain resolves or the total 100 mL of the mix are used. Therefore, the MB rinse is 3 total rinses per day, 6 hours apart.

Unused MB will be returned to Investigational Pharmacy Services at MDACC by the study staff for future incineration in accordance with the current SOP.

6.5 Data collection

Patients enrolled in the study will be asked to complete a baseline assessment questionnaire in person, including the Modified Harris mucositis-related pain assessment tool. The patient will have subsequent follow-up interviews at 1, 2, 7 days with repeat assessment of the Modified Harris mucositis-related pain assessment tool. Furthermore, on Baseline, Day 0, Day 1, Day 2, Day 7 and Day 30, adverse event will be assessed, and this maybe by telephone or face-to-face in the clinic. The patient's medication use will also be assessed at follow-up, including morphine equivalent daily dose (MEDD) and other reported analgesics used for the treatment of their mucositis-related pain. Lastly, the research team will investigate if any patient reported any side effects from the treatment.

All completed data will be stored electronically in the MD Anderson REDCap system, in a locked file, on password-protected computers. Only research team members will access the files. Subject registration will be entered into CORe database.

6.51 Modified Harris mucositis-related pain assessment tool (MHMPAT)

Among the numerous scales utilized for assessment of mucositis, most do not incorporate pain. The original Harris mucositis-related pain assessment tool was developed to fill the void of inadequate assessment of mucositis associated pain in existing assessment tools (18). The scale includes the NRS, which is one of the most widely utilized pain assessment measures in research and clinical care (17). Its use is related to its ease of administration. It uses an 11-point scale for measuring pain intensity (0 representing no pain, to 10 representing the worst possible pain). It is also beneficial for the current study, as it can accurately assess pain during telephone interview (17).

For this study we developed the Modified Harris mucositis-related pain assessment tool which has not yet been validated but incorporates aspects of many validated tools. It has been adapted with permission from the creator, Debra J. Harris, RN, MSN, and OCN.

7.0 Data Analysis

Demographic information along with effectiveness data will be used to determine if there is a difference between the conventional care alone and the use of MB in addition to conventional care for the treatment of intractable pain associated with oral mucositis.

7.1 Sample Size Justification and Randomization

In a one-way ANOVA study, sample sizes of 15, 15, 15, and 15 are obtained from the 4 groups whose means are to be compared. The total sample of 60 subjects achieves 83% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means is represented by their standard deviation which is 1.14 (means of 0, 2, 2.5, and 3 for conventional therapy, conventional therapy + MB 0.025, conventional therapy + MB 0.05, and conventional therapy + MB 0.1, respectively). The common standard deviation within a group is assumed to be 2.5. We will conduct stratified randomization by baseline pain (baseline NRS 0-5 vs. 6-10) and oral functioning score (0-3 vs. 4-6).

7.2 Primary Outcome Analysis

Descriptive statistics (means (SDs) or counts (percent)) will be used to summarize demographics, disease, and treatment variables according to the intervention arm. Potential differences between the arms based on demographic, disease, and treatment variables will be explored using Chi-square test or Fisher's exact test for categorical variables and ANOVA or Kruskal-Wallis test for continuous variables, depending upon the nature of the variables being investigated.

Our primary endpoint is the reduction in pain scores assessed within the NRS component of the Modified Harris mucositis-related pain assessment tool from baseline to 7 days which is considered the end of the study. The mean change in scores will be compared among 4 arms, utilizing ANOVA. If there are significant differences between intervention arms in some covariates, a linear regression model will be utilized to compare arms by adjusting for those significant covariates. The mean pain scores over time will be compared among study arms, utilizing linear mixed effects models. Covariates that showed significant differences among study arms will be adjusted in the linear mixed effects models. Two separate analyses, intention to treat and per protocol, will be conducted for primary analysis. Tukey's pairwise comparison will be conducted if a significant difference is observed among 4 arms Intention to treat analysis population will include all patients who were randomized to one of treatment groups regardless of completion of the treatment. Per protocol analysis will include those patients who completed the treatment originally allocated. Patients who did not have 7day NRS will be replaced.

Patients who were initially enrolled in conventional arm and crossed over to one of MB arms will be included in assigned MB arm.

7.3 Secondary Outcomes Analysis

The mean change, from baseline to 7 days, in the Modified Harris mucositis-related pain assessment tool scores and the mean change in oral functioning scores will be compared between study arms, utilizing ANOVA or Kruskal-Wallis test (eat, swallow, talk: unable=2, difficulty=1, able=0. Oral functioning score is the total score of 3 categories, ranged 0-6). We will also determine if there are any differences between arms in presence or absence of pain, pain scores, overall analgesic use (including opiate use primarily used for oral mucositis pain via MEDD measurement), and the incidence of untoward side effects utilizing ANOVA, Kruskal-Wallist, Chi-square test, or Fisher's exact test as appropriate. In addition, to obtain a measure of compliance with MB treatment, we will compare the dropout rate within the MB group to the dropout rate in the conventional therapy group utilizing Chi-square test or Fisher's exact test.

The Investigator is responsible for completing an efficacy/safety summary report and submitting it to the IND office Medical Monitor for review. This should be submitted after the first 5 evaluable patients per arm, complete 7 days of study treatment, and every 5 evaluable patients per arm, thereafter.

In addition, the Patient Drug Administration log will be used to keep the record of drug usage. Duration of pain relief corresponding to each drug use will be collected during the interview, in person for Day 0 and via telephone for Day 1, Day 2, and Day 7**.** The number of MB doses needed (during the last 24 hours or since the last follow-up) in order to achieve pain relief will be collected on Day 1, Day 2, and Day 7.

7.4 Data Confidentially, Entry, and Storage

All data gathered in this study will be strictly confidential using anonymous identifiers. Research staff will conduct data entry. This database will be stored utilizing the password-protected MD Anderson REDCap system and accessed only by members of the research team. Data will be entered electronically and analyzed.

8.0 Adverse Events Reporting

8.1 Adverse Events (AEs)

All patients will be monitored through weekly in person or by phone calls by the research staff allowing for close monitoring of potential adverse events during treatment. In addition, patients will be given a contact phone number for treatment-related questions.

Research staff will collect toxicity, symptoms, and adherence to study medication schedule weekly. Treatment-related toxicities (NCI Common Terminology Criteria for Adverse Events, version 4) will be monitored by the research staff.

Grade 1 and Grade 2 AEs will not be reported. AEs that are Grade 3 and above that meet the definition for serious adverse events (SAEs) in Section 8.2 will be considered to be serious adverse events (SAEs) and will be reported. SAEs that are unexpected and related (definitely, probably, or possibly related) to MB use will be reported promptly according to institutional policies (see below). SAEs that are either expected or unexpected but unrelated (unrelated or unlikely to be related) to MB use will be summarized on the continuing review report. The principal investigator and the treating physician will determine whether or not an AE is related to the study medication.

If in the course of assessing symptoms, the patient reports severe symptoms, the data collector will determine if the patient's healthcare provider is aware that the patient is experiencing this severe symptom. If the healthcare provider is not aware, the data collector will determine if the patient intends to inform the healthcare provider of the symptom and its severity within 24 hours. If the patient does not intend to inform the health care provider, the data collector will inform the patient that the data collector will let the health care provider know of the severity of the symptom within 24 hours. If in the course of assessing symptoms, the data collector becomes aware of any imminently life-threatening condition that the patient is experiencing, the data collector will let the patient know that data collector will be informing a healthcare provider immediately of the condition. The data collector will then initiate contact with a healthcare provider immediately.

A list of adverse events known to be associated with primary treatment is listed in section 3.2 of the protocol.

8.2 Serious Adverse Events (SAEs)

8.21 Definition

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes.

1. Death
2. A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly/birth defect.
6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient

hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

8.22 Reporting SAEs

1. Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
2. All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
3. **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted **within 24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
4. **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB**.
5. **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**
6. **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**
7. **Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.**
8. **It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

   The MD Anderson "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the MD Anderson IRB.

8.3 Unblinding

In the event of an SAE or an emergency situation that is likely due to the symptom trial agent as determined by the treating physician or PI, the investigational pharmacy at MD Anderson will be asked to unblind the symptom trial agents for the affected study subject. Pharmacy staff will proceed with unblinding and will contact the PI with the agent information so that

the treating clinicians can appropriately manage the SAE and confirm the specific source of the SAE. All incidents of unblinding will be documented by the study team and will also be maintained on file in the MD Anderson Investigational Pharmacy for reference. The Principal Investigator will notify protocol IRB, DSMB and IND medical monitor if unblinding of subject occurs.

9.0 Criteria for Removal from the Study

- Development of an SAE related to the study drug.
- Discontinuation of cancer cares at MD Anderson Cancer Center.
- Pregnancy during the study period.
- Completion of study.

10. References

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