Oral Ondansetron versus Transdermal Granisetron (Sancuso) for Women with Cervical, Endometrial or Vaginal Cancers Receiving Pelvic Chemoradiation

1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 To measure response rates to anti-emetic therapy (no emetic or retching episodes and no rescue medication use) in the late onset phase (days 4-7) of Granisetron (Sancuso) administered via a transdermal patch compared to orally administered Ondansetron in women with cervical, endometrial or vaginal cancer undergoing chemoradiation therapy.

1.2 Secondary Objectives

1.2.1 To measure response rates to anti-emetic therapy (no emetic or retching episodes and no rescue medication use) in the acute (0-24 hours) phase of Granisetron administered via a transdermal patch compared to orally administered Ondansetron in women with cervical, endometrial or vaginal cancer undergoing chemoradiation therapy.

1.2.2 To measure response rates to anti-emetic therapy (no emetic or retching episodes and no rescue medication use) in the delayed (24-72 hours) phase of Granisetron administered via a transdermal patch compared to orally administered Ondansetron in women with cervical, endometrial or vaginal cancer undergoing chemoradiation therapy.

1.2.3 To measure compliance with Granisetron administered via a transdermal patch compared to orally administered Ondansetron in women with cervical endometrial or vaginal cancer undergoing chemoradiation therapy.

1.2.4 To measure amount and effect of nausea/vomiting on quality of life with Granisetron administered via a transdermal patch compared to orally administered Ondansetron in women with cervical endometrial or vaginalcancer undergoing chemoradiation therapy.

1.2.5 To determine if Granisetron administered via a transdermal patch compared to orally administered ondansetron results in less dose reductions of cisplatin in women with cervical, endometrial or vaginal cancer undergoing chemoradiation therapy.

1.2.6 To measure amount of “rescue medication” for chemotherapy-induced nausea and vomiting (CINV) during chemoradiotherapy in women with cervical, endometrial or vaginal cancer undergoing chemoradiation therapy taking Granisetron administered via a transdermal patch compared to orally administered Ondansetron.

1.3 Exploratory Objective

1.3.1 Women undergoing definitive chemoradiation therapy for cervical, endometrial or vaginal cancer typically have significant diarrhea as a therapeutic complication. However, 5HT3 blockers tend to cause constipation as a medication side effect. Therefore, we hypothesize that women undergoing chemoradiation therapy and receiving the continuous administration of a 5HT3 blocker via the patch (Sancuso) will have less diarrhea than those receiving only 72 hours of scheduled oral 5HT3 blockers (ondansetron)

2.0 BACKGROUND AND RATIONALE

Worldwide, there will be over 500,000 new cases of cervical cancer diagnosed this year which makes *cervical cancer the second most common cause of cancer death among women*. Multiple phase III trials have shown that platinum-based chemotherapy given with radiation therapy in the treatment of cervical cancer improves disease-free and overall survival when compared with radiotherapy alone (1-3). As a result of these studies, the National Cancer Institute (NCI) in 1999 issued a clinical alert changing the standard-of-care from radiotherapy alone to radiotherapy with concurrent platinum based chemotherapy

in the treatment of locally advanced cervical cancer (4). Based on these data showing improved survival for patients with cervical cancer receiving concurrent cisplatinum with pelvic radiation, most providers have begun adding cispltinum to pelvic radiation for patients with vaginal cancer. AT MD Anderson, we frequently prescribe concurrent cisplatinum with pelvic radiation for women with vaginal cancer as part of our standard of care. In these women with vaginal cancer receiving chemoradiation, the cisplatinum dosage and schedule as well as the radiation treatment plan are the same as in women with cervical cancer. In addition to chemoradiation therapy as primary or adjuvant therapy for patients with cervical and vaginal cancers, combination cisplatinum and pelvic radiotherapy are commonly used in the adjuvant setting for intermediate and high risk patients with endometrial cancer after hysterectomy and staging. In these women with endometrial cancer receiving adjuvant chemoradiation, the cisplatinum dosage and schedule as well as the radiation treatment plan are also the same as in women with cervical and vaginal cancers.

Unfortunately, cisplatin, the agent most commonly administered with radiation therapy, is a well-known emetogenic agent. In a recent phase II study of cisplatin with radiotherapy in women with cervical or endometrial cancer, 100% reported symptoms of nausea with over two-thirds experiencing grade 2 or 3 toxicity (5). The National Comprehensive Cancer Network (NCCN) lists cisplatin among the “highly emetogenic agents” causing chemotherapy induced nausea and vomiting (CINV) in over 90% of patients who do not receive antiemetic therapy after drug infusion. The current recommendations from the NCCN for women receiving cisplatin is to start an anti-emetic therapy prior to starting chemotherapy and to continue for at least 72 hours after administration of infusion as the risk of emesis and nausea for persons receiving cisplatin lasts for at least 4 days.

At MD Anderson Cancer Center and Lyndon B. Johnson General Hospital (LBJ), we typically prescribe oral antiemetic therapy with a 5HT3 blocker to start with chemotherapy and continue the medication on a scheduled “around the clock” regimen for three days after chemotherapy administration (institutional standard of care). However, up to 27.5% of women receiving chemotherapy will report nausea or emesis on the fourth day after chemotherapy and another 16.5% will report these symptoms on the fifth day after administration (6) (late onset nausea/vomiting) when scheduled anti-emetic therapy has been discontinued. In addition, women receiving cisplatin as part of their treatment for cervical, endometrial or vaginal cancer do so every 7 days which means they are scheduled to take antiemetic treatment for 3 days out of every week. This frequent self-administration of anti-emetic medications only adds to the treatment burden these women are undergoing.

Recently, a new formulation of granisetron in extended release patch (Sancuso) has been shown to be equivalent to scheduled oral administration of ondansetron (Zofran). Instead of thrice daily oral administration of this 5HT3 blocker, Sancuso provides nausea relief with a single patch that is changed every 7 days. The week long duration of the patch is appealing in its potential to reduce late onset nausea and vomiting in women receiving cisplatin with concurrent radiation. We hypothesize that women receiving weekly cisplatin with pelvic radiation therapy as definitive treatment for cervical, endometrial or vaginal cancer will have less late onset nausea and vomiting (days 4-7) when given Sancuso when compared to oral ondansetron (Zofran) administration. In addition, we believe that patients will have much higher compliance and satisfaction with the once weekly patch formulation of ondansetron when compared with the thrice daily oral administration.

Two studies have evaluated transdermal vs oral granisetron. The first was a randomized phase II study of 210 patients with cancer undergoing moderately ematogenic chemotherapy. There was no difference in total and complete control of nausea, severity of nausea and vomiting or number of emetic episodes in the acute setting (<72 hours after chemotherapy). The most common side effect was headache (3.4% in granisetron patch group, 4.7% in oral granisetron group) and only 1 patient in the granisetron patch group had the patch fall off. The second study was a phase III randomized control study of oral vs. transdermal granisetron in 641 patients undergoing moderately or highly ematogenic chemotherapy. There was no difference between the two groups in the control of nausea and vomiting in the acute phase (i.e. <72

hours after chemotherapy). Constipation was the more common side effect in the patch group (6.6% of patients compared to 3.1% in the oral group.

Chemoradiotherapy with concurrent cisplatin as treatment for cervical or endometrial cancer is an ideal model for a phase III trial of an extended release delivery system of anti-emetic therapy (i.e. Sancuso patch) for the following reasons:

1. CINV from cisplatin is severe and lasts up to 7 days after chemotherapy administration.
2. Cisplatin is administered on a weekly basis making 72 hours of scheduled oral antiemetic therapy 3 days out of every week burdensome.
3. Cisplatin with external beam radiation therapy is only given for 5 weeks establishing a definitive endpoint to rotate subjects off protocol.
4. Cervical cancer is a disease that effects women, and female gender increases risk of CINV (7). In addition, the median age at diagnosis is younger than for most other cancers. Young age is also a risk factor for increased CINV (7).
5. Cervical cancer typically affects women of low socioeconomic status and poor education where understanding and compliance with scheduled anti-emetic drug regimens may be an issue, which could adversely impact delivery of curative therapy.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

- 3.1.1 Women with cervical, endometrial or vaginal cancer dispositioned to receive primary or postoperative adjuvant pelvic radiation therapy with concurrent cisplatin administration.
- 3.1.2 Women must be at least 18 years of age.
- 3.1.3 Women must be able to read English or Spanish at a sixth grade level.
- 3.1.4 Women with childbearing potential must have a negative pregnancy test within 1 week of starting chemoradiation therapy.

3.2 Exclusion Criteria

- 3.2.1 Women with cervical endometrial, vaginal cancer who are receiving chemotherapy and/or radiation therapy for recurrent disease.
- 3.2.2 Women with cervical, endometrial or vaginal cancer who are receiving extended field radiation therapy
- 3.2.3 Women with cervical, endometrial or vaginal cancer who are receiving chemotherapy and/or radiation therapy in a palliative setting.
- 3.2.4 Women with cervical, endometrial or vaginal cancer who have already received their first dose of chemotherapy or have received more than 7 days of radiation

4.0 THERAPEUTIC PROGRAM

This phase III study will randomize eligible patients with cervical, endometrial or vaginal cancer undergoing chemoradiation therapy (see above for eligibility criteria) to receive either 34.3 mg of granisetron formulated in a transdermal patch (Sancuso) replaced every 7 days (Group A) **OR** 8 mg of ondansetron orally thrice daily starting with cisplatin administration and continued for 72 hours after chemotherapy infusion (Group B). Patients may not be enrolled on study if they have already started their chemotherapy treatment or have received more than 7 days of radiation prior to starting their chemotherapy.

In addition, data on compliance/ease of administration, amount of nausea and vomiting, and effect of nausea and vomiting on quality of life will also be collected. These data will be collected weekly via self-administered questionnaires that are estimated to take < 5 minutes to complete.

Study Drug and Dosage Schedule

Group A: 34.3 mg of granisetron formulated in a transdermal patch (Sancuso) replaced every 7 days. Patients will have the transdermal patch placed/replaced prior to the IV infusion of cisplatin. At cycle 1, patients will receive IV ondansetron 8mg prior to IV cisplatin. Administration of transdermal patch will be at the start of IV cisplatin. For subsequent cycles, replacement of transdermal patch will start during the premedication period of IV cisplatin.
Group B: 8 mg of ondansetron orally thrice daily starting within 8 hrs of cisplatin administration and continued for 72 hours after chemotherapy infusion.

Cisplatin and premedications will be given per standard order sets and physician discretion.

4.1 Evaluation During Study

All treatments will occur within one week time frame +/- 3 days to allow for scheduling. The patient will be given pill diaries for transdermal patch and/or Odansetron, rescue medications, and anti-diarrheal medications. Adverse event monitoring and concomitant medications will be recorded prior to each cycle and one week after the last cycle. QOLs will be completed prior to each cycle and one week after the last cycle. Lab work and chemoradiation will be ordered at the discretion of the treating physician.

4.2 Duration of treatment

Treatment will last 5 cycles or until the patient withdraws (Section 8.0), whichever comes first. The patient may continue to receive further chemoradiation after 5 cycles at the discretion of the treating physician; however, the patient will be taken off treatment after 5 cycles.

The transdermal patch and Ondansetron should be continued as scheduled even if the IV Cisplatin is held.

4.3 Study Endpoints

Primary Endpoint:

1. The proportion of patients with a complete response (CR; defined as no emetic or retching episodes and no rescue medication use) during the late onset phase (4-7 days post-chemotherapy) measured during cycle 1 of chemoradiation therapy.

Secondary Endpoints:

1. The proportion of patients with a complete response (CR; defined as no emetic or retching episodes and no rescue medication use) during the acute phase (0–24 h post-chemotherapy) measured during each cycle of chemoradiation therapy.
2. The proportion of patients with a complete response (CR; defined as no emetic or retching episodes and no rescue medication use) during the delayed phase (24–72 h post-chemotherapy) measured during each cycle of chemoradiation therapy.
3. Ease of administration/compliance of two medications measured during each cycle of chemoradiation therapy.
4. Effect of nausea/vomiting on quality of life (Osoba Module – Appendix D) measured prior to each cycle of chemoradiation therapy and one week after the last cycle. Amount of nausea/vomiting in the prior week (Morrow Assessment of Nausea and Emesis (MANE Scale) – Appendix C) measured prior each cycle of chemoradiation therapy and one week after the last cycle
5. The number of dose reductions/patient during the 5 week treatment measured prior to each cycle of chemoradiation therapy.

6. The amount of “rescue medications” utilized during the 5 week treatment, including 1 week after the last cycle of cisplatin, measured during each cycle of chemoradiation therapy.

Exploratory Endpoint:

1. The amount of diarrhea experienced weekly by the patient will be graded according to CTC 4.0 and via pill counts of anti-diarrheal medication measured each cycle.

5.0 STATISTICAL CONSIDERATIONS

This is a randomized trial to compare oral Ondansetron (OO) and Granisetron patch (GP) for control of delayed nausea and vomiting in patients undergoing chemoradiation for the treatment of locally advanced cervical, endometrial or vaginal cancer. The primary outcome is response to anti-emetic therapy (no emetic or retching episodes and no rescue medication use) in days 4-7 of the first cycle of chemotherapy.

Patients will be randomized between OO and GP using a Bayesian adaptive algorithm. (8) Technical details of this methodology are given in the "Technical Details" section below. The first 40 patients will be randomized fairly between the 2 treatment arms. Beginning with the 41st patient and as the trial progresses and data accrue the randomization will become unbalanced in favor of the therapy that, on average, has better results in terms of treatment failure, so that each successive patient is more likely to receive the treatment showing better results.

We will enroll at least 75 and at most 150 patients at an expected rate of 5 patients per month. We will enroll up to 30 patients in LBJ. With treatment OO we expect a treatment failure rate of 0.2750. (6) With treatment GP we hope to improve the treatment failure rate to 0.1375 (i.e., reduce the treatment failure rate by half).

Beginning with the 76th patient the trial will be stopped early and a treatment selected as being "superior" if the probability is 0.925 or more than one treatment's failure rate is lower than the other treatment's failure rate. If all 150 patients are enrolled, then a treatment will be selected as being "superior" if the probability is 0.915 or more than one treatment's failure rate is lower than the other treatment's failure rate. In addition, accrual to a treatment arm will be suspended if there is less than a 0.10 chance that the treatment failure rate is less than 0.225 for that treatment arm.

The operating characteristics of this study design are summarized in Table 1 below, and are based on 10,000 simulations of the trial for each scenario. From this table we can see that if the true treatment failure rates are 0.2750 and 0.1375 for OO and GP, respectively, then the probability that we will select GP as superior to OO is 0.799, and we expect to be able to reach this conclusion with an average of 35.4 + 61.9 = 97.3 patients. Also, in this scenario there is only a 0.006 chance that we would select OO as superior to GP, but there is a 0.195 chance that we would conclude that neither treatment is superior to the other.

If the true treatment failure rate is 0.275 for both treatment arms, then the probability that we will select GP as superior to OO is only 0.103, and we expect to be able to reach this conclusion with an average of 48.9 + 49.2 = 98.1 patients. Also, in this scenario there is a 0.101 chance that we would select OO as superior to GP, but there is a 0.796 chance that we would conclude that neither treatment is superior to the other.

Analysis

Once the trial is completed we will report the probability that GP has a lower treatment failure rate than OO during the late onset phase. We will also estimate the treatment failure rate for each treatment arm during the late onset phase of the first cycle of therapy with a 95% credible interval.

We will estimate with 95% confidence intervals the treatment failure rates for each treatment arm during the first 24 hours (acute phase) and during the 24-72 hour period (delayed phase) of each cycle of therapy. We will similarly estimate the treatment failure rates during the late onset phase for each cycle following cycle 1 of therapy. A treatment success is defined as no emetic or retching episodes and no rescue medication use.

We will tabulate the responses to the 4 items of the Morisky Medication Adherence (Compliance) measure for each treatment group by cycle of therapy. We will compare the 2 treatment groups with respect to the responses to each item of this instrument with a chi-square test. We will use descriptive statistics to summarize the elements of the Morrow Assessment of Nausea and Emesis (MANE Scale) and for pill counts/compliance for each treatment group by cycle of therapy. We will also use repeated measures analysis of variance methods to model compliance over all cycles of therapy.

We will use descriptive statistics to summarize the total scores for the Osoba Module, used to measure the effect of nausea and vomiting on quality of life, for each treatment group by cycle of therapy. We will compare the treatment groups with respect to the Osoba Module score with a Mann-Whitney test. We will also tabulate the responses to each of the 5 questions of the Osoba Module for each treatment group. We will also use repeated measures analysis of variance methods to model the effect of nausea and vomiting on quality of life over all cycles of therapy.

We will use descriptive statistics to summarize the number and amount of dose reductions for each treatment group for each cycle of therapy. We will also use repeated measures analysis of variance methods to model the number and amount of dose reductions over all cycles of therapy. We will similarly analyze the number and doses of rescue medications and the amount of diarrhea experienced over the course of therapy.

Technical Details
We assume a beta (1.1, 2.9) prior distribution for the treatment failure rate for each treatment. This prior distribution has a mean of 0.275 and a standard deviation of 0.200. As the trial progresses these prior distributions will be updated with the data that have accrued.

Let F_{OO} and F_{GP} be the treatment failure rates for treatments "Oral Ondansetron" (OO) and "Granisetron Patch" (GP), respectively. Prior to enrolling the 40th and subsequent patients we will calculate the randomization probability as follows. We will first calculate π_{GP} (data) = Pr($F_{GP} < F_{OO}$ | data) and π_{OO} (data) = 1 – π_{GP}(data). The randomization probability for GP will then be defined as $r_{GP} = \frac{\sqrt{\pi_{GP}}}{\sqrt{\pi_{GP}}+\sqrt{\pi_{OO}}}$, and the randomization probability for OO will be $r_{OO} = 1 - r_{GP}$.

Accrual to treatment arm OO will be suspended if Pr($F_{OO} < 0.225$ | data) < 0.10. Similarly, accrual to treatment arm GP will be suspended if Pr($F_{GP} < 0.225$ | data) < 0.10. If at any point during the trial π_{GP} (data) > 0.925 (< 0.075) the trial will be terminated and treatment "Granisetron Patch" will be selected as superior (inferior). If the maximum number of patients is enrolled in the trial and π_{GP} (data) > 0.915 (< 0.085) treatment "Granisetron Patch" will be selected as superior (inferior).

6.0 REGISTRATION AND RANDOMIZATION

All eligible patients will be required to provide informed signed consent before randomization and will be registered in CORe. Randomization will be performed using the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is maintained by the Department of Biostatistics. Research personnel responsible for enrolling and randomizing patients on this trial will be trained by the study statistician in the use of the website, with particular attention to the importance of updating patient outcomes. Access to the website is gained through usernames and passwords.

Table 1. Operating Characteristics of Study Design			
	Neither	Oral Ondansetron	Granisetron Patch
True Probability of Failure	---	0.2750	0.1375
# Patients Treated Avg (2.5%-tile, 97.5%-tile)	---	35.4 (21, 67)	61.9 (39, 102)
Pr(Selected)	0.1950	0.0060	0.7990
Pr(Selected Early)	---	0.0060	0.7740
Avg Trial Duration		19.6 months	
True Probability of Failure	---	0.2750	0.1750
# Patients Treated Avg (2.5%-tile, 97.5%-tile)	---	42.4 (22, 75)	64.0 (34, 101)
Pr(Selected)	0.4266	0.0154	0.5620
Pr(Selected Early)	---	0.0149	0.5340
Avg Trial Duration		21.6 months	
True Probability of Failure	---	0.2750	0.2250
# Patients Treated Avg (2.5%-tile, 97.5%-tile)	---	48.1 (24, 83)	59.0 (29, 97)
Pr(Selected)	0.6783	0.0487	0.2730
Pr(Selected Early)	---	0.0454	0.2520
Avg Trial Duration		21.7 months	
True Probability of Failure	---	0.2750	0.2750
# Patients Treated Avg (2.5%-tile, 97.5%-tile)	---	48.9 (26, 88)	49.2 (25, 88)
Pr(Selected)	0.7960	0.1010	0.1030
Pr(Selected Early)	---	0.0093	0.0927
Avg Trial Duration		19.8 months	
True Probability of Failure	---	0.2750	0.3250
# Patients Treated Avg (2.5%-tile, 97.5%-tile)	---	47.9 (28, 88)	40.1 (23, 76)
Pr(Selected)	0.7757	0.1910	0.0333
Pr(Selected Early)	---	0.1730	0.0298
Avg Trial Duration		17.7 months	

7.0 ADVERSE EVENTS

7.1 DEFINITIONS

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to treatment or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment.

A treatment-emergent AE is defined as any event not present prior to treatment or any event already present that worsens in either intensity or frequency following treatment.

All AEs that occur after treatment during the study must be reported in detail in the patient's source/chart and followed to satisfactory resolution or until the local Principal Investigator or Co-Investigator deems the event to be chronic or the patient to be stable. The description of the AE will include the onset date, , date of resolution, severity, seriousness, , and the likelihood of relationship of the AE to study treatment.

Severity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0(CTC AE v4.0),

If an adverse event occurs which is not contained in the CTC AE v4.0, the five-point scale below will be used:

1. Mild: discomfort noticed but no disruption of normal daily activity.
2. Moderate: discomfort sufficient to reduce or affect daily activity.
3. Severe: inability to work or perform normal daily activity
4. Life Threatening: represents an immediate threat to life
5. Death

7.2 COMMON ADVERSE EVENTS

The most common adverse events from study treatment include:

- Constipation
- Diarrhea
- Nausea
- Headache
- Drowsiness/tiredness

7.3 LABORATORY TEST ABNORMALITIES

Laboratory test value abnormalities will not be reported as AEs, unless there is an associated clinical condition for which the patient is given treatment, concomitant treatment is altered or the event is considered a serious adverse event.

7.4 SERIOUS ADVERSE EVENTS

An SAE is defined as any event that:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical

judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Reporting requirements:

Any AE considered serious or which meets the previous criteria must be reported to the study chair within one business day from the time that study personnel first become aware of the serious adverse event.

All reported SAEs (related or not to the treatment) will be followed until satisfactory resolution or until the attending physician deems the event to be chronic or the patient to be stable. SAEs will be reported till 30 days from completion of primary therapy.

7.5 ADVERSE EVENT REPORTING

Information regarding AEs will be collected from the time the patient signs the informed consent form up to 1 week post treatment., unless the AE meets the criteria as described above.
All AEs reported or observed during the study will be recorded as an AE in the patient's source/chart. Information to be collected includes:

- Type of event
- Onset
- Investigator-specified assessment of severity and relationship to treatment
- Resolution of the event
- Grade
- Any required treatment or evaluations

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be recorded. All AEs will be followed to adequate resolution. Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study it should be recorded as an AE.

7.6 OBTAINING ADVERSE EVENT INFORMATION

At every study visit, patients will be asked a standard non-leading question to obtain any medically related changes in their well-being. In addition to patient or Investigator observations, AEs will be documented from any data collected (e.g., laboratory values, physical examination findings), or other documents that are relevant to patient safety.

7.7 ASSESSMENT OF CAUSALITY

The Investigator's assessment of an AE's relationship to treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association to the AE will be characterized using the following classification and criteria:

- **Unrelated:** This relationship suggests that there is no association between the treatment and the reported event.
- **Possible:** This relationship suggests that treatment caused or contributed to the AE, i.e. the event follows a reasonable temporal sequence from the time of treatment and/or follows a known response pattern to the treatment, but could also have been produced by other factors.

- **Probable:** This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and the likely association of the event with the treatment. This will be based upon the known or previously reported complications to the treatment, or judgment based on the Investigator's clinical experience.
- **Definite:** This relationship suggests that a definite causal relationship exists between the treatment and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

7.8 ASSESSMENT OF SEVERITY

Adverse Event severity will be rated by the Investigator as mild, moderate, or severe using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

8.0 PATIENT WITHDRAWAL

Patients will be advised that they may voluntarily withdraw from the study at any time, for any reason and it will not affect their medical care. However, in such cases, appropriate effort will be made by the Investigator to determine the reason for voluntary withdrawal from the study and to document reason for withdrawal in the medical record, if known.

The last known status of these patients will be reported with the study results and all attempts to locate patients lost to follow up will also be documented.

Patients will be informed that, should they withdraw from the study, they should remain under the care of an appropriately experienced physician until the physician deems further follow-up unnecessary.

The following are circumstances for which a patient would be identified as not continuing her participation in the study:

- Study Completed / Terminated
- Death
- Voluntary Withdrawal
- Unable to Return
- physician discretion
- Intolerable toxicity
- Other

If a patient relocates to another geographic area, which requires a change of physician, reasonable attempts will be made to locate and request cooperation from that physician in order to complete follow-up.

In many instances patient withdrawal from the study constitutes a cessation of treatment. In these cases, permission should be obtained from patients by study staff to continue monitoring their disease state (relapse, survival, toxicity etc.) via patient records as this is a crucial component of the study for which consent was originally obtained.

9.0 ADMINISTRATIVE CONSIDERATIONS

The following administrative items are intended to guide the conduct of the trial.

9.1 CONFIDENTIALITY

All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient or the patient's guardian, except as necessary for monitoring by regulatory authorities, or the IRB.

The Investigator and all employees and co-workers involved with this study shall not disclose or use for any purpose, other than performance of the study, any data, records or other unpublished, confidential information disclosed to those individuals for the purpose of the study.

9.2 MODIFICATION OF THE PROTOCOL

The TMC must review and approve any changes in this research activity. Amendments to the protocol must be submitted in writing to the Investigator's IRB for approval prior to patients being enrolled into an amended protocol.

9.3 INFORMED CONSENT

A written informed consent shall be obtained from each patient prior to the patient's entrance into the study. Before recruitment and enrolment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. The Investigator will inform the patient of the purpose of the study, randomization of study groups and the follow-up schedule. The Investigator will discuss foreseeable risks involved, as well as potential benefits that result from the treatment. The Investigator will inform the patient that her medical records will be subject to review by government authorities, and by the IRB.

The patients will be informed by the Investigator that they are free to refuse participation in this study and, if they choose to participate, that they may withdraw from the study at any time without compromising further medical care.

Once the Investigator is assured that the individual understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form. The Investigator shall provide a copy of the signed informed consent to the patient.

9.4 PROTOCOL VIOLATIONS AND DEVIATIONS

The Investigator or designee should document and explain any deviation from the approved protocol. The Investigator may deviate from the protocol to eliminate an immediate hazard to trial patients without prior IRB approval. As soon as possible after such an occurrence, the Investigator should submit the implemented deviation or change, the reasons for it to the IRB if required.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the IRB and agreed to by the Investigator. Deviations usually impact individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a significant added risk to the patient, when the patient or Investigator has failed to adhere

to major protocol requirements, or when there is non-adherence to regulatory authorities' regulations and/or ICH Good Clinical Practice (GCP) guidelines The Investigator should notify the IRB of protocol violations and deviations in accordance with the IRB requirements.

10.0 STUDY CONDUCT

The study will be conducted according to the principles of the ICH E6 Guideline on GCP and the principles of the World Medical Association Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

11.0 REFERENCES

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