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STUDY TITLE:	Open-label, Randomized, Controlled, Phase 3 Safety and Efficacy Study of Trans Sodium Crocetinate (TSC) with Radiation Therapy and Temozolomide in Newly Diagnosed Glioblastoma (GBM) Biopsy-Only Subjects
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SYNOPSIS

Title	Open-label, Randomized, Controlled, Phase 3 Safety and Efficacy Study of Trans Sodium Crocetinate (TSC) with Radiation Therapy and Temozolomide in Newly Diagnosed Glioblastoma (GBM) Biopsy-Only Subjects
Protocol No.	100-206
Study Phase	3
Study Design	Open-label, randomized, controlled, phase 3 safety and efficacy registration trial. Subjects will be randomized at Baseline to the standard of care for first-line treatment of GBM plus Trans Sodium Crocetinate (TSC) or the standard of care. The standard of care for GBM will consist of temozolomide plus radiation therapy (RT) for 6 weeks followed by 28 days of rest followed by 6 cycles of post-radiation temozolomide treatment. TSC will be administered during both the RT and post-radiation temozolomide treatment periods to those subjects so randomized. During the RT treatment period subjects will receive: 1. Focal RT delivered as 60Gy/30 fractions scheduled at 2Gy/day for 5 days each week (Monday through Friday) for 6 weeks. 2. Temozolomide 75 mg/m^2 orally once daily (usually administered the night preceeding each RT session) starting the evening before the first RT session over a period of 42 calendar days with a maximum of 49 days. 3. TSC 0.25mg/kg IV for 3 days each week (e.g. Monday, Wednesday, Friday or other schedule that supplies at minimum 3 TSC doses per week) administered between 45 to 60 minutes prior to each RT session. Pneumocystis carinii pneumonia (PCP) prophylaxis is required during Temozolomide + RT administration, regardless of lymphocyte count, and is to continue until recovery of lymphocyte count to less than or equal to Grade 1. During the 28-day rest period all subjects will receive no treatment.

	During the post-radiation 6-cycle temozolomide treatment period subjects will receive: All subjects will receive: 28-day oral temozolomide (150 mg/m^2 first cycle and 200 mg/m^2 all subsequent cycles as tolerated) administered on Day 1-5 (Monday through Friday) of each 28-day cycle. Controls: Will receive oral temozolomide at night at home per the standard of care. Subjects randomized to TSC: Will receive TSC 1.5 mg/kg (or the dose recommended by the DSMB) 1.5 to 2 hours before their temozolomide dose during the daytime for 3 days during the first week of each 28-day cycle (Days 1, 3, 5: e.g. Monday, Wednesday, Friday or other schedule that supplies at minimum 3 TSC doses per week). Long-acting antiemetics may be administered prior to daytime temozolomide dosing on Days 1, 3, 5. In accordance with the FDA directive of August 22, 2017 the safety, tolerability and PK of TSC at doses between 0.25 mg/kg and up to 1.5 mg/kg in combination with conconmitant temozolomide will be assessed via a dose escalation run-in prior to initiaing the randomized trial. The first eight (8) subjects enrolled in the 100-206 trial will be assigned (not randomized between treatments) at Baseline to undergo RT plus temozolomide plus TSC treatment (0.25 mg/kg) for 6 weekly cycles followed by 4 weeks of rest in standard fashion. At the Week 10 clinic visit the same eight (8) subjects will be assigned to treatment with 2 subjects each assigned to TSC at doses of 0.25, 0.50, 1.0 and 1.5 mg/kg. More than eight (8) subjects may need to be enrolled to achieve eight (8) who complete two full cycles of temozolomide adjuvant treatment. The first eight (8) subjects will be studied in parallel and all for two full 28-day cycles with inclusion of appropriate blood sampling collection for TSC and temozolomide PK. The Data Safety Monitoring Board (DSMB) will examine the resultant safety data after 2 full cycles (Weeks 11 through 18 of post-radiation temozolomide treatment period; Days 1 to 56).

	The eight (8) subjects that are a part of the dose-escalation run-in will continue at their assigned TSC dose (0.25, 0.5, 1.0, 1.5 mg/kg) for the Week 19 TSC dosing period. The DSMB will recommend an acceptable TSC dose, if different than 1.5 mg/kg, for the post-radiation temozolomide treatment period prior to the Week 23 TSC dosing period for the eight (8) subjects that are a part of the dose-escalation run-in. Thereafter, subjects will enter the 100-206 trial and be randomized at Baseline between TSC plus standard of care or the standard of care.
Study Population	To be eligible for the study, subjects must be 18 to 70 years of age, male or female and have histologically confirmed GBM. Biopsy-only subjects with measurable contrast enhancing disease with limited disturbance of tumor during biopsy are included. Gross total resection, partial resection and debulking GBM subjects are excluded. Local surgical and pathology reports will constitute adequate documentation for study inclusion. Adequate hematologic, renal and liver function testing must be completed within 5 weeks of randomization under this protocol. Subjects must not have had prior RT, chemotherapy, immunotherapy, biologic therapy, or hormonal therapy for their brain tumor. Subjects must have a KPS $\geq$ 60, and subject or subject healthcare power of attorney must provide written informed consent.
Number of Subjects	Up to 300 will be screened; 264 randomized to complete 236 subjects.
Study Centers	Up to 100 sites
Objective	To assess the safety and efficacy of TSC as first-line treatment for biopsy-only GBM when administered with the standard of care consisting of RT/temozolomide for 6 weeks, followed by 28 day rest followed by post-radiation temozolomide-only treatment for six 28-day cycles.

Study Overview	Subjects will be randomized to TSC plus standard of care or standard of care only as the contemporaneous control, at Baseline. The study is not blinded because a sham treatment in this study is considered both ethically unsound, extraordinarily challenging given the highly colorized test article, and that all key outcome measures are objective. The start of RT treatment is recommended to begin >3 but ≤ 5 weeks after biopsy. All subjects will be given RT for 30 fractions, as tolerated. TSC treatment may continue as long as the subject is receiving RT, regardless of whether temozolomide has been discontinued or not administered. Baseline procedures will include medical history, physical exam, clinical chemistries, including CBC with differential and platelet count, urinalysis, and 12-lead ECG. An MRI scan must be performed ≤ 7 days before the start of RT. An MRI performed according to the International Standardized Brain Tumor Imaging Protocol (BTIP) 4 weeks after completion of concurrent radiation and temozolomide treatment (Week 10) will serve as the Baseline scan for assessment of response and progression for use in mRANO assessments. MRI scans will be then be performed at 8 week intervals (Weeks 18, 26, 34) through Week 34 and thereafter at approximately 8 week intervals per standard of care through Week 106. Assessment of the MRI results will be done by independent central imaging review in a blinded manner. If no tumor is present, tumor size will be recorded as zero. The concomitant use of corticosteroids (permissive stable dose or decreasing dose), anticonvulsants and other chemotherapy agents as part of the subject's treatment plan for GBM will be documented. The EQ-5D-5L instrument will be used to assess health related quality of life.
PK/PD Substudy	In accordance with the FDA directive (end-of-phase 2 meeting, August 2015), a pharmacokinetic (PK) and pharmacodynamic (PD) substudy will be performed in a subpopulation of all subjects receiving TSC.

	The pharmacokinetics of TSC will be evaluated using Population PK methodologies. The Population PK analysis will include an assessment of covariates, (e.g., subject demographics). An evaluation of exposure-response (PK/PD) will be performed for relevant safety and efficacy endpoints.
Safety Assessments	Adverse events will be graded and promptly recorded according to the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4 during the study and up to 30 days following the completion of TSC study drug dosing. Safety assessments will include physical exam, concomitant medication usage, vital signs, 12-lead ECG, and clinical chemistries, including CBC and urinalysis. Progression of disease and disease-related death will not be considered adverse events. Adverse events that occur $\geq$ 30-days after the last dose of TSC will not be collected as part of the study database. Documentation of concomitant medications $\geq$ 30-days after the last dose of TSC will be limited to corticosteroid, bevacizumab, chemotherapy, and anticonvulsant use.
Statistical Analysis Plan	Primary Efficacy Endpoint: • Overall survival (OS) Secondary Efficacy Endpoints: • Progression Free Survival (PFS); per RANO 2010 and modified RANO (mRANO 2017) • Objective Response Rate (ORR); per RANO 2010 and modified RANO (mRANO) 2017 • Karnofsky Performance Scale (KPS) • Quality of Life –EQ-5D-5L - subject reported outcome • Corticosteroid use • Anticonvulsant medication use • Chemotherapy for recurrent glioma • Changes in peripheral neuropathy, leukopenia, thrombocytopenia - graded according to CTCAE

	Exploratory Endpoints • Evaluate tumor growth kinetics of measurable target lesions • Time to unequivocal progression of enhancing non-target lesions Safety: • Adverse events • Physical exam • Concomitant medication usage • Vital signs • 12-lead ECG • Clinical laboratory Safety assessments will be made at Baseline (Day 1), during the RT treatment period, prior to the post-radiation temozolomide treatment period (Week 10), and during the post-radiation temozolomide treatment period (Weeks 11 through 34). The Sponsor will collect all radiological images for all randomized subjects, for independent central imaging review in a blinded manner. Secondary radiographic endpoint assessments includes the assessment of PFS and ORR using both RANO and mRANO as secondary endpoints. The pre-treatment MRI scan will be used as the baseline comparison scan per RANO criteria while the Week 10 post-treatment MRI will be used as baseline for all subsequent follow-ups using mRANO. An independent Data Safety Monitoring Board (DSMB) will be established to review the safety profile during the dose-escalation run-in and recommend the dose of TSC for the post-radiation temozolomide treatment period (if different than 1.5 mg/kg), review the safety profile relative to the established stopping rule and generally safeguard the interests of study participants. The details regarding the functioning of the DSMB will be outlined in the DSMB charter.

RANO/mRANO results were not included in results section. Please see rationale immediately below:

The 100-206 trial included a 19-patient lead-in dose escalation study to assess safety and tolerability. This was to be followed by a randomized study during which RANO/mRANO assessments would be performed. The Sponsor did not have adequate resources to fully support the randomized portion of the 100-206 study and commencement of enrollment in the randomized portion of the trial was suspended.

- Vital signs
- 12-lead ECG
- Clinical laboratory

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is an open-label, randomized, controlled, safety and efficacy phase 3 registration study in adults with newly diagnosed GBM (biopsy-only).

To be eligible for the study, subjects must be 18 to 70 years of age, male or female, and have histologically confirmed GBM. Biopsy-only with measurable contrast enhancing disease with limited disturbance of tumor during biopsy are included. Gross total resection, partial resection and debulking GBM subjects are excluded. Local surgical and pathology reports will constitute adequate documentation of histology for study inclusion.

Adequate hematologic, renal and liver function testing must be completed within 5 weeks of randomization. Subjects must not have had prior RT, chemotherapy, immunotherapy, biologic therapy, or hormonal therapy for their brain tumor(s). Subjects must have a KPS $\geq$ 60. Subject or subject caregiver with healthcare power of attorney must provide written informed consent. Treatment under this protocol should begin >3 but $\leq$ 5 weeks after surgery.

All procedures to qualify the subject should be completed within 5 weeks of randomization. Those assessments include physical exam, clinical chemistries, including a CBC with differential and platelet count, medical resonance imaging (MRI) scans, urinalysis, 12-lead ECG and medical history. Subjects will be assigned to treatment arms sequentially in chronological order.

Radiation plus Temozolomide Treatment (RT)
RT treatment is recommended to begin >3 but $\leq$ 5 weeks after biopsy. All subjects will receive standard-of-care RT and temozolomide ± TSC for 6 weeks. Subjects will receive TSC 0.25mg/kg IV plus the standard of care or only the standard of care for 3 days each week (e.g. Monday, Wednesday, Friday, or other schedule that supplies at minimum 3 TSC doses per week) and all receive SOC for the other 2 days (Tuesday, Thursday) for 6 weeks (maximum of 49 days) administered between 45 and 60 minutes before the start of RT.

Rest
After 6 weeks (30 fractions) of RT and temozolomide, subjects will have a 28-day rest.

Post-Radiation Temozolomide Treatment Period
During the post-radiation temozolomide treatment period subjects will receive:

All subjects will receive: 28-day oral temozolomide (150 mg/m^2 first cycle and 200 mg/m^2 all subsequent cycles as tolerated) administered on Day 1-5 (Monday through Friday) of each 28-day cycle.

Controls: Will receive oral temozolomide per the standard of care.

Subjects randomized to TSC: will receive TSC 1.5 mg/kg, 1.5 to 2 hours before each temozolomide dose during the daytime, for 3 days during the first week of each 28-day cycle (Days 1, 3, 5: e.g. Monday, Wednesday, Friday, or other schedule that supplies at minimum 3 TSC doses per week). Long-acting antiemetics may be administered prior to daytime temozolomide dosing on Days 1, 3, 5.

The study design is shown in Table 5.

Table 5. Study Design

Diagnosis / Screening **≤ 4 weeks prior to randomization (minimum 21 days)**
• Suspected brain tumor • Diagnostic Brain MRI • Brain biopsy • Histologic confirmation of GBM (locally reviewed) • Subject treatment plan includes RT and temozolomide • Informed consent • Demographics, medical history, physical exam, vitals, ECG, lab, KPS, pregnancy test

Baseline / Stratification / Randomization (maximum 14 days)
• Pre treatment, post 49iopsy MRI ≤ 7 days prior to randomization • Perform any remaining tests or repeat of tests ≤ 7 days prior to randomization • Randomization prior to treatment
• Stratification
• Age ≤ 60, > 60
• Multiple tumors versus Single tumors
• IDH status (IDH-mutant, IDH-wt)

RT Treatment
• RT treatment recommended to begin >3 but ≤5 weeks after biopsy • Treatment with SOC RT/temozolomide ± TSC for 6 weeks

Rest
• No treatment for 4 weeks

Week 10
• 10 week MRI (4weeks after the conclusion of RT at week 6) per BTIP to be used as the Baseline comparison scan for assessment of PFS and ORR per mRANO criteria

Chemotherapy Only Treatment
• Treatment with SOC temozolomide for six 28-day cycles ± TSC • TTF per Investigator SOC

Follow Up
• Follow subject until death

3.2 Study Population

3.2.1 Subject Population

Newly diagnosed GBM biopsy-only subjects who meet all inclusion and exclusion criteria.

3.2.2 Inclusion Criteria

1. Male or female subjects who are at least 18 to 70 years of age
2. Have histologically confirmed GBM
3. The only surgical consideration is biopsy. Subjects who had gross total resection, partial resection and/or debulking are excluded.
4. Measurable (>10mm x 10mm) contrast enhancing disease.
5. Limited disturbance of tumor during biopsy
6. Surgical and pathology reports that document surgery was limted to biopsy and histologic confirmation
7. Life expectancy of at least 3 months.
8. Subjects must have a Karnofsky score (KPS) of ≥ 60 at Screening.
9. Glucocorticoid therapy allowed.
10. Tumor Treatment Field (TT Fields) therapy allowed.
11. If female, the subject must have a negative serum or urine pregnancy test at Screening unless meeting non-productive potential criteria.
12. Subjects must have hematologic and renal functions as specified: Absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, Hgb ≥ 9.0g/dL, creatinine ≤ 1.7mg/dL, total bilirubin ≤ 1.5mg/dL, blood urea nitrogen (BUN) within 2 times the upper limit of normal, transaminases ≤ 4 times above the upper limits of the institutional norm.
13. The subject or subject's medical power of attorney has provided written consent to participate in this study.

3.2.3 Exclusion Criteria

Subjects are not eligible if they meet any of the following criteria:

1. Subjects who had gross total tumor resection, partial resection, and/or debulking surgery.
2. Subjects must **not** have had prior RT, chemotherapy (including Gliadel wafer), immunotherapy or therapy with a biologic agent, or hormonal therapy.
3. Subject who is pregnant or lactating.
4. Subject with a serious concurrent infection or medical illness that would jeopardize the ability of the subject to receive study treatment with reasonable safety.
5. Subject who cannot undergo MRI.
6. Subject receiving concurrent chemotherapeutics or investigational agents within 30 days of study entry, including gliadel wafers or gliasite application.
7. Subjects with other uncontrolled medical conditions, e.g. myocardial infarction, cerebrovascular accident, diabetes or hypertension

8. Subjects diagnosed with another malignancy within 3 years prior to study start with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma, non-melanomatous skin cancer or carcinoma in situ of the uterine cervix
9. CTCAE Version 4, Grade 4 non-hematological toxicity (except for alopecia, nausea, vomiting).

3.2.4 Women of non-reproductive potential

A woman is of non-reproductive potential if the woman meets 1 of the following conditions:

- At least 2 years post-menopausal
- Hysterectomy
- Bilateral oophorectomy
- Tubal ligation

3.2.5 Acceptable Methods of Birth Control

Women of reproductive potential must use a double method of birth control through 30 days after the last dose of test article (Week 34) or temozolomide. Subjects must use 2 of the following acceptable methods of birth control as applicable:

- Oral, transdermal, or implanted hormonal contraceptives at a stable dose for at least 2 months prior to Randomization
- Intrauterine device
- Diaphragm with spermicide
- Male condom

The concomitant medication and/or medical history documentation including that recorded on the eCRF for females of reproductive potential should support contraceptive usage, as applicable.

3.3 Withdrawal of Subjects

3.3.1 Stopping Rules

The Data Safety Monitoring Board will examine the safety profile of TSC at prescribed time points during the trial per the DSMB charter.

In addition, if $\geq$ 2 of first 10 subjects in the randomized portion of the trial are unable to complete $\geq$ 75% of the RT due to toxicity related to the addition of TSC to RT and temozolomide the study will be stopped and the overall safety of TSC added to RT and temozolomide re-assessed.

3.3.2 Criteria for Early Withdrawal

The following events are considered sufficient reason to discontinue a subject from the study:

- Subjects are free to withdraw from the study at any time, for any reason, and without prejudice.

- The subject is non-compliant.
- The subject experienced an adverse event (AE) that in the investigator's opinion precludes continued participation.
- The subject incurred a significant protocol violation that constitutes a safety hazard or significantly confounds the interpretation of the data from that subject.
- At the Sponsor's request.
- The study is terminated.

3.3.3 Procedures for Discontinuation

The Sponsor's Medical Officer or designee will be notified of the discontinuation of any subject as soon as feasible, either prior to or after the subject discontinues. For subjects that withdraw, the Follow-up Visit assessments should be completed. The reason for discontinuation must be recorded in the case report form (CRF). If the subject discontinues due to an AE, the investigator should follow the AE until resolution or until the investigator and Sponsor (designated Medical Monitor) agree that no further follow-up is warranted. If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol, if possible.

3.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Lab values may be reassessed during the study defined screening period without being considered as rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

3.4.1 Subjects Lost to Follow-up

The investigator will attempt to contact any subject that fails to return in order to evaluate the reason the subject has not returned and to obtain follow-up safety information. All attempts to contact the subject should be documented via registered letter with return receipt.

3.4.2 Replacement of Subjects

Only randomized subjects who did not receive any TSC and did not receive a RT session will be replaced. Subjects who have received TSC and/or at least 1 session of RT will not be replaced.

6.1 Populations

The intent-to-treat (ITT) population will include all subjects randomized. The primary analysis will be conducted on the ITT population, with subjects grouped according to randomized treatment, regardless of treatment actually received.

The safety population will include all subjects who received any treatment on study. Subjects in the safety analyses will be grouped according to treatment actually received.

6.2 Subject Disposition

At the end of the study, a disposition or reason for discontinuation will be recorded for all enrolled subjects. The frequency with which subjects leave the study for a given reason will be summarized descriptively by treatment group. Continued treatment with TSC beyond that will not be offered.

6.3 Demographics and Baseline Characteristics

Demographic characteristics at baseline such as age, race, and gender will be summarized descriptively.

6.4 Efficacy Analysis

6.4.1 Primary Efficacy Analysis

Overall Survival

The primary objective of this study is to determine whether TSC in combination with SOC RT and temozolomide chemotherapy improves overall survival in newly diagnosed GBM biopsy-only subjects relative to SOC alone. Overall survival will be calculated from randomization to the time of death from any cause. Subjects with unknown survival status will be either censored administratively at the time of the primary analysis or the time of last known survival status will be used.

Overall survival will be estimated in time-to-event fashion using Kaplan-Meier methods. Survival rates at 6, 12, 18 and 24 months will also be calculated with corresponding 95% confidence intervals. Median OS will be calculated for each treatment arm.

Analysis of stratification factors will include:

- Age ≤ 60, > 60
- Multiple or single tumor(s)
- IDH status (IDH-mutant, IDH-wt)

6.4.2 Secondary Efficacy Analysis

Progression Free Surival (PFS)
Confirmed PFS will be analyzed similarly to OS in time to event fashion. Assessments will be as defined by RANO and mRANO criteria.

For RANO analysis, the pre treatment, post biospy MRI ≤ 7 days prior to randomization will be considered the Baseline. To determine progression events, follow-up MRI scans performed at Weeks 10, 18, 26, 34, 42, 50, 52, 58, 66, 74, 82, 90, 98, 106 will be compared to the pre-treatment MRI. RANO does not require confirmation of progression, therefore the date of the event is the date of the first instance of PD.

For mRANO analysis, the Week 10 MRI scan will be considered the Baseline.To determine progression events, follow-up MRI scans performed at Weeks 18, 26, 34, 42, 50, 52, 58, 66, 74, 82, 90, 98, 106 will be compared to the Week 10 scan. In order to be considered a true progression event, the progression must be confirmed per the mRANO criteria. The date of the event is the date of the first instance of PD (preliminary PD). Follow-up MRIs in accordance with mRANO to separate true progression from pseudoprogression will be done since pseudoprogression was evident in the Phase 2 trial, but not accounted for in PFS determination.

Objective Response Rate (ORR)
Durable objective response rate (CR and PR) will be estimated via radiological assessment using RANO and mRANO

For RANO analysis, the pre-RT and pre-temozolomide MRI will be considered the Baseline. For mRANO analysis, the Week 10 MRI scan will be considered the Baseline. Both RANO and mRANO require confirmation of response. To be considered a true response, the response must be maintained until the next MRI scan at least 4 weeks later. The first instance of reponse is considered confirmed, or durable, and would represent the date of response.

The secondary endpoints of PFS and ORR will be evaluated if the primary endpoint is statistically significant. A Bonferroni correction will be included in the analysis of PFS and ORR to control the overall false positive rate. Improvements in PFS and ORR will be considered statistically significant if the p-value in a 2-sided test is less than 0.025. Patient Reported Outcome (PRO) will not be considered an endpoint for product labeling.

Karnofsky Performance Scale (KPS)
Functional status will be evaluated using KPS.

Quality of Life (QOL) –European Quality of Life Questionnaire (EQ-5D-5L)
EQ-5D-5L is a standardized, non-disease specific instrument for describing health status (Herdman et al. 2011). EQ-5D system consists of two parts: the EQ-5D descriptive system and the visual analog scale (VAS). The EQ-5D descriptive system includes 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension

comprises 5 levels (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). The VAS records the respondents' self-rated health status on a vertical graduated (0-100) VAS. The EQ-5D data will be scored as described by McDowell and Newell (1996). A higher score represents a better health status. QOL data will be analyzed and presented descriptively by treatment arm.

Corticosteroid, Anticonvulsant and Chemotherapy for Recurrent Glioma
Concomitant use of corticosteroids, anticonvulsants, and other chemotherapy agents as part of the subject's treatment plan will be documented throughout the study. Response will also be evaluated by stable or decreasing concomitant corticosteroid use and chemotherapy agents needed as part of the subject's treatment plan for recurrent glioma. These data will be analyzed and presented descriptively.

Adverse Events of Special Interest
Given that TSC may positively impact several adverse events common to the standard of care, appearance and changes in leukopenia, thrombocytopenia and peripheral neuropathy will be analyzed and presented descriptively and will be graded according to CTCAE.

6.5 Safety Analysis

No formal statistical hypothesis testing will be performed with regard to safety variables. The safety assessments will include the collection of adverse events, physical exam, concomitant medication usage, vital signs, 12-lead ECG, and clinical laboratory.

Adverse Events
The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for AE reporting. Adverse events will be coded using the MedDRA coding dictionary. Summaries of treatment emergent adverse events will be reported overall, by severity and by relationship to study drug. Incidence rates will be reported by body system, organ class and preferred term by treatment arm. Progression of disease including death will not be considered an AE. AEs that occur beyond 30-days after the last dose of test article (Week 34) will not be collected as part of the safety database.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment.

Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the start of study treatment until 30-days after the last dose of test article, as well as at the time points specified in the Schedule of Events. SAEs will be collected from the start of treatment until the last follow-up visit.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as pre-existing conditions on the Medical History section of the case report form (CRF).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

Method of Detecting AE and SAE

Care will be taken not to introduce bias when detecting an AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Follow-up of AE and SAE

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.

Regulatory Reporting Requirements for SAE

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other relevant regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.