STATISTICAL ANALYSIS PLAN v2.5

(replaces SAP v2.4, 15 December 2020)

SPONSOR:	Elios Therapeutics, Inc.
PROTOCOL TITLE:	A prospective, randomized, blinded, placebo-controlled, phase IIb trial of an autologous tumor lysate (TL) + yeast cell wall particles (YCWP) + dendritic cells (DC) vaccine vs unloaded YCWP + DC and embedded phase I/IIa trial with tumor lysate particle only (TLPO) vaccine in stage III and stage IV (resected) melanoma to prevent recurrence.
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1 Rationale for study design

Based on our prior phase I/IIa clinical trials in stage IV melanoma, the resected stage IV patients enjoyed the greatest benefit from vaccination. As such, stage III and IV (resected) patients are the target population for this adjuvant trial. Prevention of recurrence is the primary objective.

2 Study Endpoints

2.1 Primary Endpoint

- To determine 24-month disease-free survival (DFS) in vaccinated vs. control patients in the intention to treat (ITT) and per protocol (PP) population as defined in section 4.2.2.

2.2 Secondary Endpoints

- To determine DFS and overall survival (OS) at 36 months in vaccinated vs. control patients in the ITT and PP population.
- To determine DFS and OS at 36 months in vaccinated vs. control patients who received concurrent CPI.
- To determine DFS and OS at 36 months comparing patients who received TLPLDC produced from 120 mL of blood vs TLPLDC produced after G-CSF.
- To determine DFS and OS at 24 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients
- To determine DFS and OS at 36 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients
- To determine DFS and OS at 36 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients comparing patients who received concurrent CPI.
- To determine DFS and OS at 36 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients comparing patients who received TLPLDC produced from 120 mL of blood vs TLPLDC produced after G-CSF.
- To document the safety of the vaccine, assessed by CTCAEv4.03.

3 Trial Overview

The primary aim of the present trial is to evaluate the efficacy of TLPLDC as an adjuvant treatment for resected stage III and IV melanoma. The primary endpoint of this trial will be DFS at 24 months in the ITT and PP population. Secondary endpoints include DFS and OS at 36 months in the ITT and PP populations and safety of the vaccine. Endpoints will also be analyzed to compare vaccine manufacturing method and/or presence of adjuvant check point inhibitors. Approximately 120 patients will be randomized in a 2:1 ratio to receive vaccine or placebo. The embedded phase I/IIa trial of TLPO vs. TLPLDC will randomize patients 2:1 to TLPO or TLPLDC. Given that the patients will be randomized between the TLPO phase I/IIa and TLPLDC, there will be an opportunity to directly compare the toxicity profile of these two vaccines. Also, the 20 additional TLPLDC vaccine patients will be assessed with the original 120 randomized patients to account for the 140 patients mentioned below in section 3.4.

3.1 Trial Design and Conduct

Stage III and Stage IV (resected) melanoma patients will be identified prior to definitive surgery and screened for inclusion/exclusion criteria. Eligible patients will be counseled and consented for tissue procurement. Enrolled patients will have their disease surgically resected and a portion (1mg minimum) of their melanoma sterilely frozen in provided freezing vials and storage tubes. This tissue will be shipped in liquid nitrogen shippers through FedEx to our central facility in Greenville, SC and stored frozen until vaccine preparation. If patients cannot be rendered disease-free, they will be considered screen failures for this study. If melanoma is being resected from multiple locations (primary and nodes, two different metastatic sites), then samples of each would be preferred but not mandatory.

As indicated by SoC per the National Comprehensive Cancer Network (NCCN) guidelines and determined by the treating team, if a patient is to receive systemic therapy (chemotherapy or IFNα and/or radiation therapy), then the vaccinations will not begin until SoC therapy is completed. Although, patients on adjuvant check point inhibitors (CPI) may start the vaccine trial after showing tolerance of the CPI for at least 3 months given that there may a synergistic benefit and no added toxicity when adding the vaccine to CPI. Once SoC therapies are complete (or demonstrating 3 months of tolerance on CPI) and the patient deemed clinically disease-free, they will be consented for treatment and randomized. Once consented, patients will receive a single injection of Neupogen (G-CSF) 300 μg (or its equivalent) SQ 24-48 hrs prior to having 70 mL of blood collected and sent to our central facility for DC isolation and preparation. Patients who cannot tolerate Neupogen, or its equivalent or refuse it, will have 120 mL of blood drawn and sent. Additional blood may be drawn if additional vaccine doses need to be made or re-made for any reason. Vaccines will be prepared by producing TL through freeze/thaw cycling and then loaded into pre-prepared YCWP. The TL-loaded YCWP will be introduced to the DC for phagocytosis thus creating the TLPLDC vaccine which will be frozen in single dose vials. Each vial will contain 1-1.5 x 10^6 TLPLDC and will be labeled with the patient's unique study number. The TLPO is created in a similar manner with the freeze/thaw cycling, loaded into pre-prepared YCWP, and then capped with silicate for stability. The TLPO vaccine is then frozen in single dose vials of 1.0 x 10^8 TLPO and will be labeled with the patient's unique study number.

Based on their randomization, autologous TLPLDC (active vaccine) or unloaded YCWP + autologous DC (control) or autologous TLPO will be sent back to the site in a blinded fashion. Upon randomization of the 120th patient the randomization will transition to 2:1 (TLPO phase I/IIa : TLPLDC). Regardless of assigned group, the site will receive 6 single dose vials to be injected intradermal monthly x 3 followed by boosters at 6, 12, and 18 months in the same lymph node draining area (preferably the anterior thigh). Patients must begin vaccinations between 3 weeks and 3 months from completion of SoC (or demonstrating 3 months of tolerance on CPI). Frozen tumor will be maintained for active vaccines for all patients to include the control patients. The latter will be offered their active vaccine at time of recurrence in a crossover fashion. Additionally, control patients who do not recur will be offered active vaccine at the completion of the trial.

Safety data will be collected on local and systemic toxicities and graded and reported per the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Disease-free status will be monitored per SoC as outlined by NCCN. Suspected recurrences will be documented with biopsy and pathologic confirmation. Time to recurrence will be based on date of randomization to time of confirmed recurrence. Recurrent patients will be offered participation in the open label portion of the study. New active vaccine will be made for all patients, and they will be inoculated at 0, 1, 2,3, 6, and 9 mos. Patients will be treated per SoC for their recurrence. Safety and tumor response will be assessed per RECIST and iRECIST on their SoC follow-up scans.

3.2 Patient Population

Patients with stage III melanoma whose disease is determined to be resectable, and stage IV melanoma patients who are rendered disease-free by surgery, will be randomized 2:1 to receive TLPLDC or placebo. Following the completion of the phase IIb portion of the study, patients with stage III melanoma whose disease is determined to be resectable, and stage IV melanoma patients who are rendered disease-free by surgery will be randomized 2:1 to receive TLPO or TLPLDC.

3.3 Treatment Arms

There will be two treatment arms for the phase IIb portion of the study evaluating TLPLDC versus placebo:

1) Vaccinated group = autologous tumor cell lysate (TL) + yeast cell wall particles (YCWP) + autologous DC (TLPLDC)
2) Control group = empty YCWP + autologous DC

There will be two treatment arms for the phase I/IIa portion of the study evaluating TLPO versus TLPLDC:

1) Vaccinated group = autologous tumor cell lysate + yeast cell wall particles (TLPO)
2) Vaccinated group = autologous tumor cell lysate (TL) + yeast cell wall particles (YCWP) + autologous DC (TLPLDC)

3.4 Sample Size Justification

Assuming a baseline recurrence rate of 60% (corresponding to a DFS of 40%) at 2 years in this mixed group of stage III and stage IV (resected) melanoma patients, a sample size of approximately 120 will have 80% power to detect a statistical difference between treatment proportions controlling the type I error at $\alpha = 0.05$ (two-sided).

A blinded evaluation of the first 75 patients enrolled discovered an early recurrence rate of 12% prior to completion of the primary vaccine series. To compensate for this early recurrence rate and preserve the power of the trial, enrollment will be extended by at least an additional 20 patients, now totaling at least 140.

After randomization of the 120th patient, the randomization will transition to 2:1 (TLPO phase I/IIa : TLPLDC) for an additional 60 patients. The TLPO vaccine group (n=40) will be assessed primarily for tolerability of the TLPO vaccine based on CTCAE v4.03 graded local and systemic toxicities. Given that the patients will be randomized between the TLPO phase I/IIa and

TLPLDC, there will be an opportunity to directly compare the toxicity profile of these two vaccines. Also, the 20 additional TLPLDC vaccine patients will be assessed with the original 120 randomized patients to account for the 140 patients mentioned above (see protocol Appendix B, Combined Trials Schema).

3.5 Randomization and Unblinding

3.5.1 Randomization Methodology

Patients will be randomized 2:1 to either the vaccine or placebo. A central, permuted block randomization scheme will be used with a selected blocking factor (block size) determined based on the proposed allocation ratio and number of subjects. The block size will be specified in the randomization plan. An Interactive Web Response System (IWRS) will be used for the randomization to either the vaccinated vaccine group or the control group.

Study staff will log into the IWRS using unique credentials and input subject-specific screening and baseline information. In accordance with the randomization schedule, the IWRS will assign the randomization number to each subject. Each subject must be given only the investigational product assigned by IWRS. The study staff will document the randomization number in the electronic Case Report Form (eCRF). Subjects are to be randomized in the order in which they qualify from the screening phase for inclusion in the study.

Upon randomization of the 120th patient in the TLPLDC phase IIb, the TLPO phase I/IIa trial will be initiated and 60 additional patients will be randomized 2:1 (TLPO phase I/IIa : TLPLDC).

3.5.2 Unblinding procedures

The investigators, study personnel, subjects, medical monitor, and clinical monitors will remain blinded throughout the study, unless safety concerns necessitate unblinding.

If a medical emergency occurs and a decision regarding the subject's clinical treatment requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Unless the medical emergency is deemed to be life-threatening, the medical monitor must first be consulted before unblinding. The Investigator would then utilize the IWRS for unblinding and the unblinding procedure will be provided in the eCRF Completion Guidelines. The date, time, and reason for unblinding must be documented in the source documents and on the applicable unblinding form in the IWRS. Investigators should note that the occurrence of a SAE should not routinely trigger immediate unblinding. If the medical monitor was not notified prior to breaking the blind, the investigator must notify the medical monitor of any and all blinds broken within 24 hours of each occurrence.

All patients will be offered open label vaccine at first sign of recurrence. Non-recurrent control patients will be given the option of receiving active vaccine upon their completion of the trial.

3.6 Schedule of Events

The Schedule of Events is defined in Appendix G of the study protocol.

4 Statistical Methodology

4.1 General Considerations

All statistical analyses will be performed using SAS® Version 9.3 or higher, unless otherwise noted. The analyses of efficacy and safety endpoints will be based on the study populations for analysis defined in section 4.2. Sensitivity analyses for primary and key secondary efficacy endpoints may be performed to test the robustness of the treatment effects observed, including comparisons of vaccine manufacturing method and/or presence of adjuvant check point inhibitors. Two-sided p-values will be presented for all statistical testing, unless otherwise noted.

Continuous variables will be summarized using descriptive statistics, which includes n (number of non-missing observations), the mean, median, standard deviation, minimum, and maximum. The minimum and maximum will be reported using the same precision as the original measurement. The mean, median, other selected percentiles, and standard deviation will be reported to one decimal place more than the precision of the original measurement. For categorical variables, descriptive statistics include frequency and percentage will be presented.

Rates of 24- and 36-month DFS will be compared using the Pearson chi-square test.

For time to event analyses, the Kaplan-Meier method will be used to estimate the quartiles (25th percentile, median and 75th percentile) of time to event variable for each treatment group, along with 95% confidence intervals (Kaplan and Meier, 1958). Kaplan-Meier event rates with 2-sided 95% confidence intervals at year 1, year 2 and year 3 will also be estimated. The hazard ratio and its 2-sided 95% CI will be estimated using Cox proportional hazards model (Cox, 1972) with treatment group as the independent variable and stratified by the randomization stratification factors.

In general, all summary tables will be supported by a relevant patient data listing including all patients enrolled into the study. The listings will include all data collected and will be sorted by patient identifier and actual visit date, as applicable, unless otherwise noted. Baseline is defined as the last non-missing valid value prior to first study treatment. Change from baseline, if presented will be the post-treatment value minus baseline value, unless otherwise noted.

Concomitant medications will be coded by the WHO Drug Dictionary and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The dictionary versions will be documented in the Data Management Plan for the study.

4.2 Study Populations for Analysis

4.2.1 Intention to Treat Population

Analyses of the ITT population will include all patients who undergo randomization. ITT analysis will be performed with each randomized patient evaluated in the treatment arm to which they are randomized regardless of actual treatment received.

4.2.2 Per Protocol Population

The per protocol (PP) population is a subset of the ITT population. Per the protocol, subjects may be excluded from the PP population for the following reasons and other as determined prior to database lock: violations of eligibility criteria, development of second malignancies, early recurrences occurring prior to completion of the first four inoculations, receiving alternate disease-directed therapy without evidence of recurrence, or major deviation from prescribed vaccination schedule (to include boosters). For the purposes of the primary statistical analysis, the PP population will include all subjects except those who experience early recurrence prior to completion of the fourth inoculation timepoint at 6 months.

4.2.3 Safety Population

The Safety Population will consist of all patients who received at least 1 dose of investigational product. In the event of study drug administration errors, analyses of the Safety Population will be performed according to the treatment the subject actually received.

4.3 Subject Disposition

All patients enrolled into the study (sign informed consent) will be accounted for in the Patient Disposition Table. Disposition information, such as the following will be summarized by the number and percentages of patients in each treatment group and overall:

- Patients who comprise the ITT, safety and PP populations
- Patients who discontinue treatment and the reason for treatment discontinuation
- Patients who discontinue the study and reason for discontinuation
- Patients who die during the study

4.4 Demographics and other Baseline Characteristics

4.4.1 Demographics

Demographics such as gender, age, race and ethnicity will be summarized descriptively by treatment group and overall for the ITT population. Demographic characteristics of all patients in the ITT and PP populations will be summarized including age, race, disease histology, tumor location, tumor depth, ulceration, number of mitoses, nodal status (number and micro- vs macrometastasis), AJCC clinical stage, location and number of distant metastases (if present), surgery extent, and other disease-directed therapies to include chemotherapy, radiation therapy, and biologic therapy.

4.4.2 Baseline Characteristics

Baseline characteristics such as the following will be summarized descriptively by treatment group and overall for the ITT population:

- Age
- Race
- Disease histology
- Tumor location
- Tumor depth

- Ulceration
- Number of mitoses
- Nodal status (number and micro- vs macro-metastasis)
- AJCC clinical stage
- Location and number of distant metastases (if present)
- Surgery extent
- Other disease-directed therapies to include chemotherapy, radiation therapy, and biologic therapy

4.4.3 Medical history

Medical History will be coded using the MedDRA dictionary terms and will be summarized descriptively by SOC and PT by treatment group and overall for the ITT population.

4.4.4 Urine Pregnancy Test

Data on urine pregnancy test (UPT) will not be summarized but will be provided as a listing.

4.5 Protocol Deviations

Protocol deviations (major and minor) will be defined prospectively prior to database lock by a review committee or medical monitor who is blinded to treatment assignment. Major protocol deviations as well as those deviations that could possibly affect the interpretation of the primary endpoint (subset of major deviations) will be tabulated by treatment group and overall. All deviations will be presented in listings.

4.6 Extent of Exposure

The number of months on study, number of injections received, and cumulative investigational product exposure will be summarized using descriptive statistics by treatment group and overall for the ITT population.

4.7 Methods for Handling Missing Data

Missing data for the binary landmark endpoint will be handled by a tipping point analysis including the following steps:

1. The data are filled in m times to generate m complete data sets.
2. The m complete data sets are analyzed by using standard procedures.
3. The results from the m complete data sets are combined for the inference.
4. Repeat step #1 to generate multiple imputed data sets, with a specified shift parameter that adjusts the imputed values for observations in the treatment group (not the placebo group).
5. Repeat step 2 for the imputed data sets with shift parameter applied.
6. Repeat step 3 to obtain the p-value to see if the p-value is still<=0.05.
7. Repeat steps 4-6 with more stringent shift parameter applied until the p-value >0.05.

Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints.

4.8 Analysis of Primary Endpoint

The primary endpoint of this study is to determine 24-month disease-free survival (DFS) in vaccinated vs control patients analyzed as a proportion. The primary efficacy analysis will be performed on the ITT and the PP population as equally important analyses given the high early recurrence rate. The Bonferroni method will be used to control the overall type 1 error rate, and the study will be considered successful if analysis in either analysis population (ITT or PP) if the two-sided p-value is less than or equal to 0.025. All stratified analyses will utilize the stratification factors as entered at the time of randomization. Analyses may also be performed using the subgroups listed in Section 4.10.

The primary efficacy analysis will also be conducted by site for the ITT and PP populations in order to explore the possibility of a treatment by investigative site interaction. Investigative sites that individually represent fewer than five subjects will be combined for this exploratory analysis; geographic region will be substituted if the average number of subjects per site is fewer than ten.

The primary analysis will be conducted 24 months after the 120^{th} patient is enrolled.

DFS will be analyzed both as a proportion and time-to-event outcome. Rates of 24- and 36-month DFS will be compared using the Pearson chi-square test. The overall type 1 error rate of 2.5% will be used for rejection of the null hypothesis in favor of the alternative hypothesis that autologous TLPLDC vaccine will have a different 24-month DFS event rate over that of unloaded YCWP + autologous DC in the ITT and PP populations. The study will be considered successful if the two-sided p-value is less than or equal to 0.025 in either analysis population (ITT or PP).

In the time-to-event analysis, DFS is defined as the time interval (months, calculated as days/30.4) from the randomization date to the date of first observation of disease recurrence (i.e., first documented evidence per radiographic analysis or per the investigator via confirmation procedure of biopsy or cytology) or death from any cause, whichever comes first.

Subjects last known to be alive, who have not experienced recurrence of disease, are censored at their last assessment date (using standard of care (SoC) assessment) for disease recurrence defined above, or at the primary analysis data cut-off date, whichever comes first. Subjects who had first disease recurrence before randomization or have no radiographic post-baseline tumor assessment, will be censored at their randomization date.

The Hazard ratio of vaccine compared with control and its 2-sided 95% confidence interval will be estimated using a Cox proportional hazards model with treatment groups as the independent variable and adjusted for the randomization stratification factors.

Kaplan-Meier curves will be used to assess DFS for each treatment group. A log-rank test stratified by the randomization stratification factors will be used to compare the treatment groups in the ITT and PP populations. Any subgroup analyses will be displayed; any p-values for individual strata will be regarded as descriptive statistics.

To explore the possibility of a treatment by investigative site interaction, the primary analysis will also be conducted by site for the ITT and PP populations. Sites that have enrolled large numbers of subjects relative to other trial centers will be identified to see if the results obtained at those investigative sites are influential. Investigative sites that individually represent fewer than 10 subjects will be combined for this exploratory analysis; geographic region will be substituted if the average number of subjects per site is fewer than 5.

4.9 Analysis of Secondary Endpoints

4.9.1 Efficacy

- To determine DFS and OS at 36 months in vaccinated vs. control patients
- To determine DFS and OS at 36 months in vaccinated vs. control patients who received concurrent CPI.
- To determine DFS and OS at 36 months comparing patients who received TLPLDC produced from 120 mL of blood vs TLPLDC produced after G-CSF.
- To determine DFS and OS at 24 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients
- To determine DFS and OS at 36 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients
- To determine DFS and OS at 36 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients comparing patients who received concurrent CPI.
- To determine DFS and OS at 36 months in TLPO vaccinated vs. TLPLDC (randomized and pooled) vs. control patients comparing patients who received TLPLDC produced from 120 mL of blood vs TLPLDC produced after G-CSF.

DFS at 36 months will be analyzed using the same methodology as the primary endpoint, both as a proportion and time-to-event outcome. Overall Survival (OS) at 36 months will be calculated as the duration of survival from randomization until the date of death from any cause. If the date of death is not available, OS will be censored at the date the patient was last known to be alive. OS will be summarized by treatment group using median, Q1 and Q3 from the KM estimate of survival. The KM survival curve will be provided as a figure.

Due to changes in standard of practice, specifically the FDA approval of checkpoint inhibitors (CPI) in the adjuvant setting, the clinical protocol was modified to allow for the inclusion of patients who had demonstrated initial tolerability to CPI. These patients were randomized and received concurrent CPI + either TLPLDC or placebo. Therefore, an additional secondary analysis will be performed specifically to assess DFS and OS in this subgroup of patients who received concurrent therapy. This analysis will be conducted using the same methodology as the primary endpoint.

DFS and OS comparing vaccinated patients who received TLPLDC produced from 120 mL of blood vs vaccinated patients who received TLPLDC produced after G-CSF to determine if there is any difference in clinical outcomes due to the different production methods. Additionally, each vaccinated group with the different production methods will be compared separately to the placebo group using the same methodology as the primary endpoint. Finally, these groups will be

compared to the placebo group in three arm analyses as well as exploratory two arm analyses by grouping like arms to generate assumptions for phase 3 planning as appropriate.

Similarly, DFS and OS comparing vaccinated patients who received TLPO in the phase I/IIa portion of the study will be compared to patients who were randomized to TLPLDC as well as placebo. The comparison to TLPLDC will be first evaluated in patients randomized to TLPLDC in the phase I/IIa portion of the study and then in a pooled manner to all patients who received TLPLDC in both portions of the study. Following this, patients who received concurrent CPI versus no concurrent CPI will be compared. To compare patients who received TLPO to TLPLDC produced from 120 mL of blood vs vaccinated patients who received TLPLDC produced after G-CSF, the following four-arm comparison will be used:

1) Vaccinated group = autologous tumor cell lysate + yeast cell wall particles (TLPO)
2) Vaccinated group = autologous tumor cell lysate (TL) + yeast cell wall particles (YCWP) + autologous DC (TLPLDC) produced from 120 mL of blood
3) Vaccinated group = autologous tumor cell lysate (TL) + yeast cell wall particles (YCWP) + autologous DC (TLPLDC) produced after G-CSF
4) Control group = empty YCWP + autologous DC

This four-arm comparison will be conducted similarly to the primary endpoint analysis with 24- and 36-month DFS and OS rates being calculated in each arm and KM estimates and figures generated. The hazard ratio of TLPO vaccine compared with each of the other three arms and the associated 2-sided 95% confidence intervals will be estimated using a Cox proportional hazards model with treatment groups as the independent variable and adjusted for the randomization stratification factors. TLPO will serve as the referent group to permit the calculation of hazard ratios among each of the other three arms.

4.9.2 Safety

To determine the safety of the vaccine, assessed by CTCAEv4.03. Safety will be determined by adverse events, physical examinations, vital signs, laboratory parameters and ECOG performance status (described in section 4.12).

4.10 Subgroup Analyses

4.10.1 Stage

Subgroup analyses will be conducted by stratifying for stage (III vs. IV). This subgroup analysis may include 24-month DFS and OS as well as 36-month DFS and OS.

4.10.2 Other subgroup analyses

Subgroup analyses may be conducted for other selected endpoints. These subgroup analyses will be descriptive in nature and may include but are not limited to the following:

- Age (18-64 years, ≥65 years old)
- Age (<60 years, ≥60 years old)
- Gender (Male, Female)
- Race

- Geographic Region

In addition, Cox proportional hazards regression models will be fit to determine the association between DFS and OS and treatment group. The secondary efficacy analysis will be performed on the ITT and PP population as co-primary analyses given the high early recurrence rate.

4.11 Interim Analysis and Early Stopping Guidelines

A Data Safety Monitoring Board (DSMB) external to the sponsor will be formed with members chosen for their expertise in oncology, melanoma, and statistical methods in clinical trials.

The primary role of the external DSMB is to protect the safety of the study participants throughout the study duration. They will accomplish this by periodically reviewing safety and efficacy analysis results in order to assess the risk-benefit profile for subjects enrolled in this study. Access to both safety and efficacy data will provide the DSMB a broad perspective with which to generate recommendations for appropriate actions. The external individuals serving on the DSMB will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias, these individuals will not have direct contact with the study site personnel or subjects.

Selected sponsor staff may serve as liaisons to the external DSMB, but will not be voting members, and will not be unblinded to the results.

The data for review are outlined in the DSMB charter and agreed to in advance by the DSMB members. Unblinded reports for review will be generated by an independent CRO that is external to the sponsor as well. The external DSMB will convene periodically, as outlined in the DSMB Charter, and the start date will depend on subject accrual rates.

An interim analysis is planned 6 months after the 120th patient is enrolled. No early stopping rule is included. There are no plans to stop the study early for efficacy, thus there are no adjustments for multiplicity.

At other interim evaluations, the DSMB will focus on safety, and will review efficacy data only to balance the risk-benefit assessment. Any specific guidelines for study stopping for safety reasons will be developed by the DSMB and documented in the DSMB Charter.

4.12 Safety Evaluation

4.12.1 Adverse Events

Treatment emergent adverse events (TEAEs) reported during the study will be listed, documenting onset, action taken, change in dosing, severity, relationship to Investigational product, severity and outcome. A treatment emergent adverse event is defined as an AE that occurs on or after the date of the first study treatment.

Verbatim terms on the eCRFs will be linked to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA).

A summary of all TEAEs by the number and percentages of subjects who experienced any of the following will be provided by treatment group and overall:

- Any TEAE, any TEAE with CTCAE severity grade > 3, any TEAEs definitely, probably or possibly related to the Investigational Product, any serious TEAEs, any AEs leading to dose reductions and drug interruptions or drug withdrawal, and AEs leading to study discontinuation.
- Any fatal TEAEs, including relationship to Investigational Product (Definite, Probable, Possible)

Additionally, the number and percent of unique subjects reporting any TEAE will also be summarized by treatment group and overall, SOC and PT, seriousness, maximum CTCAE grade, relationship to Investigational Product (Definite, Probable, Possible) and AEs leading to study discontinuation or drug withdrawal. AE summaries will utilize the Safety population. For all AE summaries, if a subject has more than one AE within a PT, the subject is counted once in that PT. If a subject has more than one AE within a SOC, the subject is similarly counted once in that SOC.

4.12.2 Deaths

The number of percent of subjects experiencing death will be summarized by each treatment group and overall along with a listing of deaths and the number of days of the death since the last injection of Investigational Product.

4.12.3 Laboratory Data

Clinical laboratory tests will be evaluated for any clinically significant changes during the study period. All laboratory data (hematology and chemistry) will be listed and reported by treatment group and overall in the units recorded on the eCRFs. Shift tables by analyte and by out of range flag (high, low, normal) may be presented to facilitate the evaluation of change from baseline to each subsequent visit, in the safety population. A listing of the laboratory data will be presented including the clinical significance flag.

4.12.4 Vital Signs

Vital signs, including body mass index (BMI), weight (standardized to kg), blood pressure (mmHg), heart rate (beats/min) and body temperature (standardized to F), will be summarized by treatment group and overall. Observed values will be tabulated at baseline, and at each scheduled post-baseline scheduled visit. Change from baseline at each scheduled post-baseline time point will also be summarized. A listing of vital signs will be provided.

4.12.5 Physical Examination

Physical examination findings, including ECOG Performance Score will be summarized by treatment group and overall. Observed values will be tabulated at baseline, and at each scheduled post-baseline scheduled visit.

4.12.6 Concomitant Medications

Concomitant Medications will be coded per the WHO Drug dictionary. Concomitant Medications will be tabulated by treatment group, Drug Class (pharmacological level, ATC3) and Drug Name (chemical substance level, ATC5). These data will be provided in subject data listings along with the verbatim drug term and usage details.