STATISTICAL ANALYSIS PLAN

RAPT Therapeutics, Inc.

FLX475-03

Protocol Title:	Phase 2 Study of FLX475 in Combination with Ipilimumab in Advanced Melanoma
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1 STATISTICAL ANALYSIS PLAN APPROVAL

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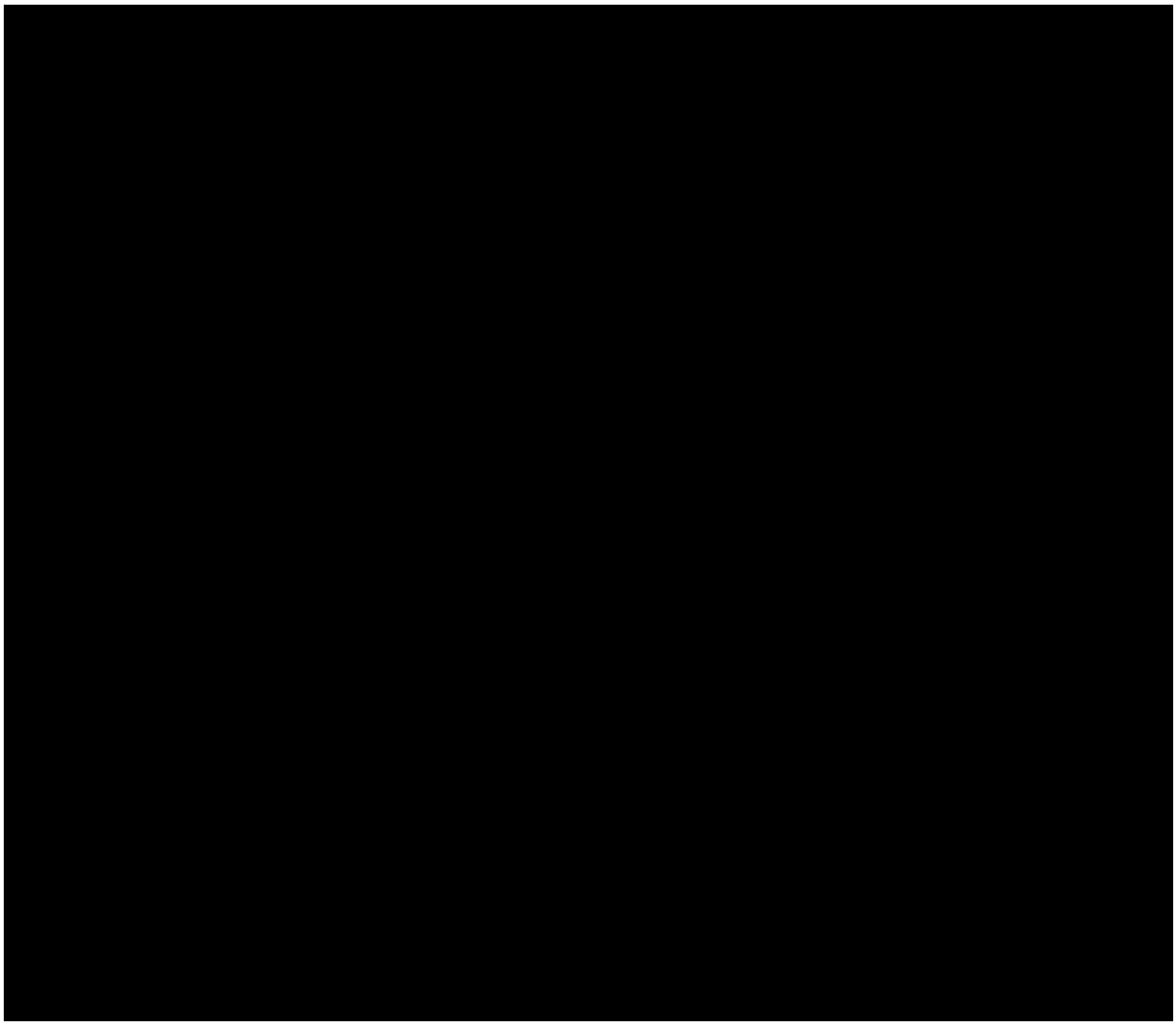

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3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AUC	Area under the plasma time-concentration curve
BMI	Body mass index
BP	Blood pressure
C_{max}	Maximum concentration
CSR	Clinical study report
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report Form
FAS	Full Analysis Set
ICH	International Council for Harmonisation
iRECIST	Modified RECIST for immunotherapies
ITT	Intent-to-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics, protocol deviation
PO	By mouth
PK	Pharmacokinetics
PS	Performance status
PT	Preferred term
Q3W	Every 3 weeks
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
WHODD	World Health Organization Drug Dictionary

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for RAPT Therapeutics, Inc. Protocol FLX475-03 (Phase 2 Study of FLX475 in Combination with Ipilimumab in Advanced Melanoma). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to data analysis and before database lock to provide full details to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

5 STUDY OBJECTIVES

5.1 Primary Study Objective(s)

The primary objectives of this study are:

- To evaluate the objective response rate (ORR), defined as confirmed complete or partial response per RECIST 1.1, of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent

- To evaluate the safety and tolerability of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent

5.2 Secondary Study Objective(s)

The secondary objectives of this study are to evaluate:

- To evaluate the progression-free survival (PFS) of subjects with advanced melanoma treated with FLX475 in combination with ipilimumab who have been

previously treated with an anti-PD-1 or anti-PD-L1 agent

- To evaluate the overall survival (OS) of subjects with advanced melanoma treated with FLX475 in combination with ipilimumab who have been previously treated with an anti-PD-1 or anti-PD-L1 agent

- To evaluate the objective response rate (ORR), defined as confirmed complete or partial response per modified RECIST for immunotherapies (iRECIST), of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent

- To evaluate the plasma concentrations of FLX475 when it is given in combination with ipilimumab

- To assess the effects of FLX475 in combination with ipilimumab on pharmacodynamic (PD) markers relating to drug mechanism of action

- To characterize the onset, magnitude, and duration of tumor control in subjects receiving FLX475 in combination with ipilimumab

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This clinical trial is a Phase 2, open-label study at approximately 3−5 investigational sites in the US to determine the anti-tumor activity of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent.

The study will be conducted starting with a safety run-in portion in which 6 eligible subjects will be enrolled and treated for at least one 3-week cycle to determine if the safety profile of FLX475+ ipilimumab is acceptable to complete enrollment of the approximately 20-subject study. Should the safety profile be deemed not acceptable for the 100 mg FLX475 PO QD and 3 mg/kg ipilimumab intravenous (IV) Q3W combination regimen, an alternative (lower) dose regimen of either or both drug(s) may be selected and tested in an additional 6-subject safety run-in phase. Ultimately at least 20 subjects should be treated and evaluated with a single chosen combination dose regimen.

Accrual to the study may be discontinued prior to completing enrollment, for reasons including, but not limited to, unacceptable safety, slow/insufficient enrollment, or changes in standard clinical practice. For each subject, the study consists of the following: screening period, treatment phase, and long-term follow-up:

- Screening visit within 21 days of enrollment into the Treatment Phase

- Treatment Phase comprising up to a maximum of 4 cycles (4 doses) of ipilimumab and up to 35 treatment cycles (2 years) of FLX475, unless another intervening reason for discontinuation occurs. Each treatment cycle is 3 weeks in duration. Treatment beyond 35 cycles may be considered only if it is felt to be in the best interests of the subject by the investigator and upon Sponsor agreement (if feasible)

- End-of-treatment visit within 90 days after the final dose of study treatment

- Posttreatment survival follow-up phase

The definition of the end of the study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

The study will start with a safety run-in phase. The first six subjects enrolled and treated at the recommended Phase 2 dose of FLX475 (100 mg/dose QD) plus ipilimumab (3 mg/kg IV q3W, up to 4 doses) will be followed for at least one 3-week cycle (21 days) to monitor for any unacceptable (or dose-limiting) toxicities prior to enrolling additional subjects.

After the first six subjects enrolled have completed the 3-week safety observation period, a Safety Review Committee (SRC) will be convened. The SRC members will comprise appropriate Sponsor and contract research organization (CRO) representatives, including the Sponsor's medical monitor or designee(s), safety officer or designee, and clinical trial managers (CTMs). Additional members may be added as needed (e.g. Pharmacokinetics (PK) scientist and/or biostatistician). The SRC will carefully consider all available safety, laboratory, and PK information in consultation with the study investigators. After review of all available data, the SRC may recommend continued enrollment of the entire study (e.g. if no unacceptable toxicities are observed); dose reduction of either FLX475 and/or ipilimumab; or discontinuation of the study. Beyond the safety run-in phase, the SRC will continue to meet at least quarterly during the study to review accumulating safety data and may also recommend an amendment to the protocol to evaluate alternate study drug administration schedules or other changes in study design as may be appropriate based on emerging clinical data.

6.2 Schedule of Assessments

For the complete schedule of assessments, refer to Section 11.6 of the protocol.

6.3 Treatments

6.3.1 Treatments Administered

Subjects will take FLX475 orally once daily (QD) starting on Day 1 of Cycle 1. See Section 6.3.1.1.1 for details of the planned dose administration schema.

Subjects will also receive ipilimumab. Ipilimumab 3 mg/kg will be administered IV Q3W for up to four doses.

The treatments to be used in this study are outlined in Table 2.

Table 2 Study Treatments

Study Treatment	Formulation	Dose Levels	Route of Administration	Sourcing
FLX475	Tablets	100 mg (with possible dose reduction to 75, 50, or 25 mg) QD	Oral	Provided centrally bythe Sponsor
Ipilimumab	Solution for infusion	3 mg/kg Q3W	IV infusion	Provided bythe site

IV = intravenous, Q3W = once every 3 weeks, QD = once daily.

6.3.1.1 FLX475 Administration

All subjects will take FLX475 orally once daily on a continual basis. On days when ipilimumab is also administered (i.e., Day 1 of Cycles 1−4), FLX475 should be taken approximately 1 hour before the ipilimumab infusion.

The dose administration schema for FLX475 is provided below, along with instructions for dose modification.

6.3.1.1.1 Dosing Plan

As noted in Section 6.1.4 of the protocol, the recommended Phase 2 dose of FLX475 of 100 mg PO QD has been selected both for monotherapy and for combination therapy with pembrolizumab in study FLX475-02. Therefore, this same dose will be used in this study in combination with ipilimumab. Should the safety run-in safety data suggest that the 100 mg of FLX475 dose is not acceptable in combination with ipilimumab, a lower dose (e.g. 75 or 50 mg PO QD) may be chosen to be used after evaluation in a new safety run-in cohort of six subjects. In the event of a change in FLX475 dose, additional subjects may be enrolled to ensure that a minimum of 20 subjects are treated at the chosen combination dose regimen.

After all subjects in the safety run-in phase have completed the 3-week safety observation period, a Safety Review Committee (SRC) will be convened. The SRC members will be composed of appropriate Sponsor and CRO representatives, including the Sponsor's medical monitor or designee(s), safety officer or designee, and clinical trial managers (CTMs). Additional members may be added as needed (e.g., PK scientist, and/or biostatistician). The SRC will carefully consider all available safety, laboratory, and PK information in consultation with the study investigators. After review of all available data, and if the safety profile of the combination therapy is deemed acceptable, the SRC will recommend continuation of the study and enrollment of the remainder of the subjects. If the safety profile of the combination regimen is not deemed to be acceptable (e.g. dose-limiting toxicity (DLT) observed in > 1 of 6 subjects), the SRC may recommend de-escalation of FLX475 to a lower dose (e.g. 75 or 50 mg PO QD); de-escalation of ipilimumab to a lower approved dose (e.g. 1 mg/kg); delay, or termination of dosing. Beyond the safety run-in, the SRC will continue to meet at least quarterly during the study to review accumulating safety data and may also recommend an amendment to the protocol to evaluate alternate study drug administration schedules or other changes in study design as may be appropriate based on emerging clinical data.

6.3.1.2 Ipilimumab Administration

Ipilimumab 3 mg/kg will be administered as an IV infusion over 30 or 90 minutes (per institutional protocol) on Day 1 of the first four 3-week treatment cycles (i.e., 21 days [± 3 days]) after all procedures and assessments have been completed, including any 1 hour post-FLX475 dose procedures, approximately 1 hour after the Day 1 dose of FLX475.

The investigational staff should make every effort to ensure that the infusion duration be as close to 30 or 90 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and + 10 minutes is permitted.

Ipilimumab should be prepared and administered per standard institutional protocol and the approved label instructions.

6.3.2 Method of Assigning Subjects to Treatment Groups

All subjects in the study will be assigned to the treatment described in Section 6.3.1

6.4 Efficacy and Safety Variables

6.4.1 Efficacy Variable(s)

6.4.1.1 Primary Efficacy Variable

Primary and secondary efficacy analyses will not be summarized due to early discontinuation of the study and a limited amount of available efficacy data.

6.4.2 Description of Safety Variables

Safety assessments will consist of monitoring and recording of all AEs and serious adverse events (SAEs) using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (Appendix 1 of the protocol), regular laboratory evaluation for hematology, blood chemistry, and urine values; regular performance of physical examinations and vital sign measurements; and periodic electrocardiograms (ECGs).

6.4.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. For this study, the study treatments are FLX475 and ipilimumab. An AE does not necessarily have a causal relationship with the medicinal product. Progression of the cancer under study is not considered an AE.

Adverse events, SAEs, and other reportable safety events must be reported to the investigator by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or radiograph) that results in symptoms, a change in treatment, or discontinuation of study treatment.
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (Baseline).
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study treatment, or withholding of study treatment, whether prescribed in the protocol or not.

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE, as well as other reportable safety events (e.g., pregnancy). Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

All AEs observed during the study will be reported on the appropriate electronic Case Report Form (eCRF).

All AEs, SAEs, and other reportable safety events, regardless of relationship to study treatment or procedure, that occur after the consent form is signed but before treatment has started, must be reported by the investigator if the event caused the subject to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to, washout or discontinuation of usual therapy, diet, or a procedure.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is ≥ 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs or events of clinical interest (ECIs) that occur from the start of treatment through 30 days following cessation of study treatment must be reported on the eCRF by the investigator. See Section 6.4.2.2 for further discussion of SAEs and ECIs.

All AEs present at time of cessation of study treatment must be followed for 90 days after the subject's final dose (or 30 days after final dose if the subject initiates new anticancer therapy), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v5.0 (Appendix 1 of the protocol). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study treatment will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study treatment caused the AE?

Not Related	A causal relationship between the study treatment and the AE is not a reasonable possibility.
Possibly Related	Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug but probably the result of another factor; not clearly the result of an external factor.
Probably Related	Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug but possibly the result of another factor; not clearly the result of another factor, disappears or decreases after discontinuation of the study drug.
Definitely Related	Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug, not the result of another factor, disappears or decreases after discontinuation of the study drug, and recurs on re-challenge (if restarted).

6.4.2.2 Serious Adverse Events, Events of Clinical Interest, and Events Associated with Special Situations

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect (in the child of a subject who was exposed to the study treatment)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Events of clinical interest (ECIs) in this study, whether serious or not, include:

1. An overdose of FLX475 or ipilimumab, as defined in Section 6.4.2.3, Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. QTcF interval ≥ 450 ms with a > 60 ms increase from baseline (defined as average QTcF value from C1D1 pre-dose ECGs)

In addition to the above ECIs, events associated with special situations include pregnancy or exposure to study treatment through breastfeeding; AEs associated with study treatment overdose, misuse, abuse, or medication error. Events associated with special situations and ECIs are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs. Any occurrences of pregnancies and exposure during breastfeeding must be reported by the investigator from the start of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier.

Serious AEs must be reported for 90 days after the subject's final dose of study treatment, or for 30 days after the final dose of study treatment if the subject initiates new anticancer therapy, whichever is earlier. Additionally, any SAE brought to the attention of an investigator at any time outside the time periods specified above must be reported

immediately to the Sponsor if the event is considered to be drug related. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study treatment administration)
- Hospitalization for administration of study treatment or insertion of access for administration of study treatment
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

If possible, blood sample(s) for the measurement of FLX475 plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

6.4.2.3 Overdose

For this study, an overdose of FLX475 will be defined as any dose ≥ 2 times the indicated dose. An overdose of ipilimumab will be defined as any dose of ≥ 3 times the planned dose. No specific information is available on the treatment of an overdose of FLX475 or ipilimumab. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.4.2.4 Pregnancy, Contraception, and Breastfeeding

FLX475 and ipilimumab may have adverse effects on a fetus in utero. Furthermore, it is not known if FLX475 or ipilimumab has transient adverse effects on the composition of sperm.

Subjects should be informed that taking the study drug(s) may involve unknown risks to the unborn baby if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (from the start of study treatment [or 14 days prior to the initiation of study treatment for oral contraception] throughout the study period up to 120 days after the final dose of study treatment). If there is any question that a subject of childbearing potential will not

reliably comply with the requirements for contraception, that subject should not be entered into the study.

If a female subject inadvertently becomes pregnant while receiving treatment with FLX475, ipilimumab or both, she must immediately discontinue study treatment. If a female partner of a male subject inadvertently becomes pregnant while the subject is receiving treatment with FLX475, ipilimumab, or both, the investigator must be informed immediately. The investigator will contact the subject at least monthly and document the status of the mother and pregnancy until the pregnancy has been completed or terminated (spontaneously or through induced abortion). See Section 11.7.2 of the protocol for reporting requirement.

It is unknown whether FLX475 or ipilimumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions of drugs in the nursing infant, females who are breastfeeding are not eligible for enrollment in this study.

6.4.2.5 Laboratory Measurements

Clinical laboratory tests to be performed are summarized in Table 5 of the protocol. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 6 of the protocol) shows the visits and time points at which blood and urine samples for clinical laboratory testing will be collected in the study.

All laboratory tests during the study will analyzed locally on the day of collection unless otherwise instructed.

Results from all hematology, clinical chemistry (including serum pregnancy test, as applicable), or urinalysis samples (including urine pregnancy test, as applicable) obtained prior to study treatment administration should be reviewed prior to administration/dispensing of study treatment at the beginning of Cycle 1, at the investigator's discretion, and upon request of the Sponsor (e.g. due to borderline or abnormal values at screening).

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 6.4.2.1 and the eCRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

6.4.2.6 Vital Signs and Weight Measurements

Vital sign measurements (i.e., systolic and diastolic blood pressure (BP) [mmHg], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of

Procedures/Assessments (Table 6 of the protocol) by a validated method. Blood pressure and pulse will be measured with the subject in the sitting position, after resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Only 1 BP measurement is needed for subjects with systolic BP < 140 mmHg and diastolic BP < 90 mmHg. If the subject's initial BP measurement is elevated (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as BP assessment. If the BP assessment (i.e., the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

6.4.2.7 Physical Examinations

Physical examinations (including a neurologic examination) will be performed as designated in the Schedule of Procedures/Assessments (Table 6 of the protocol). Documentation of the physical examination will be included in the source documentation at the investigational site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF. A symptom-directed physical examination will be performed as clinically indicated.

6.4.2.8 Electrocardiograms

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 6 of the protocol). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 x 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Data should be collected using digital machines and electronically archived. Subjects must remain undisturbed in the supine position for a period of ≥ 10 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in Section 6.4.2.1 and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

6.4.3 Description of Pharmacokinetic Variables

Plasma concentrations of FLX475 will be determined with a validated bioanalytical method, and listed and summarized by time point. No PK parameters (e.g., maximum concentration (C_{max}) and area under the plasma time-concentration curve (AUC)) will be calculated. Pharmacokinetic analysis may be summarized in a separate report and is outside the scope of this SAP.

6.4.4 Description of Pharmacodynamic Variables

Pharmacodynamic endpoints are as follows:

- Changes in immune parameters, e.g., lymphocyte subpopulations and plasma cytokines or chemokines in peripheral blood or in tumor

Pharmacodynamic analysis may be summarized in a separate report and is outside the scope of this SAP.

6.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

7 STATISTICAL METHODS

7.1 General Methodology

Data will be analyzed by Precision for Medicine biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

7.1.1 Reporting Conventions

Tables and figures will be summarized by treatment group. Tables summarizing demographics and other baseline characteristics will also include a column for all subjects combined. In general, all data collected and any derived data will be presented in subject data listings, for all screened subjects. Listings will be ordered by treatment

group, site, subject number, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, SD, median, 25th (Q1) and 75th (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the eCRF or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

7.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF.

Data collected at unscheduled visits will not be included in by-visit summaries, but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

7.1.3 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables and

figures, using the numeric value reported. Data will display on subject listings to include the sign.

7.1.4 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
    - Later date – earlier date + 1, if the earlier date is on or after the date of first dose of study drug; or
    - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12);
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25;
- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value;
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

7.2 Analysis Populations

The analysis populations are defined as follows:

- **Full Analysis Set**: All subjects enrolled in the study, also known as the “Intent-to-Treat” (ITT) population.

- **Safety Analysis Set**: All subjects who receive at least one dose of the investigational product, FLX475 (even a partial dose).

7.3 Study Subjects

7.3.1 Disposition of Subjects

Subject disposition will be summarized for all enrolled subjects by treatment group . Summaries will include the number and percentage of subjects in each analysis population, completing the treatment, discontinuing from treatment (by reason), completing the study, and discontinued from study (by reason).

7.3.2 Protocol Deviations

Protocol deviations (PDs) will be identified, logged, and reviewed during the course of the study. A determination of major versus minor PDs will be made according to the criteria outlined in the study protocol deviation review plan. A listing of all PDs will be provided. For purposes of CSR reporting, all important/major protocol deviations will be identified based on the following minimum criteria:

- Subjects who entered the study even though they did not satisfy the entry criteria.
- Subjects who developed withdrawal criteria during the study but were not withdrawn.
- Subjects who received the wrong treatment or incorrect dose.
- Subjects who received an excluded concomitant treatment.

7.3.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the Safety Analysis Set by treatment group. Gender, race, ethnicity, and baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be summarized with number and percentage presented for each category. Age, height, weight, and body mass index (BMI) at baseline will be described with summary statistics (n, mean, Std Dev, median, Q1, Q3, minimum, and maximum). BMI will be calculated as: weight (kg) / [height (cm) / 100]^2. In addition, primary cancer history will be summarized descriptively.

All demographic and baseline characteristics will be presented in a data listing.

7.4 Efficacy Evaluation

7.4.1 Primary and Secondary Efficacy Endpoints

Primary and secondary efficacy analyses will not be summarized due to early discontinuation of the study and a limited amount of available efficacy data.

7.4.2 Pharmacokinetic Analysis

Pharmacokinetic analysis may be summarized in a separate report and is outside the scope of this SAP.

7.4.3 Pharmacodynamic Analysis

Pharmacodynamic analysis may be summarized in a separate report and is outside the scope of this SAP.

7.5 Safety Evaluation

Safety analysis will be carried out for the Safety Analysis Set, to include all subjects who receive at least one dose of study drug. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to the first FLX475 dose.

7.5.1 Extent of Exposure

Extent of exposure to study treatment FLX475 will be summarized for by treatment group for the Safety Analysis Set. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. The total dose received will be determined using the drug dosing log CRF. For ipilimumab, number of infusions will be presented. A by-subject listing of FLX475 and ipilimumab administration data will be presented.

7.5.2 Adverse Events

All subjects will be assessed regularly for the potential occurrence of adverse events (AEs) from the date of informed consent to 90 days after the last dose of study treatment. The incidence of treatment-emergent adverse events (TEAEs) will be summarized and tabulated using Medical Dictionary for Regulatory Activities (MedDRA), by System Organ Class (SOC) and Preferred Term (PT). A TEAE is defined as an AE that first occurs or worsens in severity on or after the first dose of FLX475. All adverse events recorded in the eCRF will be presented in data listings.

The National Cancer Institute (NCI)/CTCAE v5.0 will be used to grade both clinical and laboratory AEs. A subject with several occurrences of the same AE will be counted once

and classified by the most severe occurrence. AEs with missing severity ratings will be classified as having unknown severity, but will be assigned Grade 3 severity for analysis and summarization.

The relationship of each AE to the study treatment will be classified as related or unrelated; an AE that is possibly, probably or definitely related to study treatment will be considered related. Any AE with an eCRF description of related will be considered related. A subject with several occurrences of the same AE will be counted once and classified as related if at least one of them is classified as related. An AE with a missing relationship to study treatment will be assumed to be related to study treatment for the purpose of analysis and summarization. Relationship of AEs to FLX475 and ipilimumab will be separately recorded and analyzed.

An overview of adverse events for the Safety Analysis Set will be provided, summarizing the incidence of the following:

- Any DLT;
- Any TEAEs; FLX475-related TEAEs; ipilimumab-related TEAEs;
- Any NCI/CTCAE Grade ≥3 TEAEs; FLX475-related NCI/CTCAE Grade ≥3 TEAEs; ipilimumab-related NCI/CTCAE Grade ≥3 TEAEs;
- Any serious TEAEs; FLX475-related serious TEAEs; ipilimumab-related serious TEAEs;
- Any discontinuation of study treatment due to TEAEs; discontinuation of FLX475 due to FLX475-related TEAEs; discontinuation of ipilimumab due to ipilimumab-related TEAEs;
- Any NCI/CTCAE Grade 5 TEAEs; FLX475-related NCI/CTCAE Grade 5 TEAEs; ipilimumab-related NCI/CTCAE Grade 5 TEAEs.

TEAE summaries by SOC and PT will be provided for the following:

- TEAEs (overall and FLX475 or ipilimumab related);
- Grade ≥3 TEAEs (overall and FLX475 or ipilimumab related);
- TEAEs leading to discontinuation of study treatment (overall and FLX475 or ipilimumab related);
- Serious TEAEs (overall and any serious FLX475 or ipilimumab related);

In addition, a summary will be provided for the number and percentage of subjects with TEAEs by the highest NCI CTCAE grade. For this summary, subjects with multiple adverse events will be counted only once by the highest NCI CTCAE grade within an SOC and preferred term.

7.5.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post treatment follow-up period, will be listed by subject, to include the primary cause of death. Serious AEs, AEs of clinical interest, and AEs associated with DLT will be provided in separate subject data listings.

7.5.4 Clinical Laboratory Evaluation

Hematology and chemistry parameters will be summarized by visit for the Safety Analysis Set. Only scheduled visit values will be included in this summary.

All clinical laboratory data will be listed by subject. Values outside the normal ranges will be flagged and toxicity grades will be displayed for relevant parameters. Hematology and chemistry measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by subject, laboratory test, and unit.

7.5.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

7.5.5.1 Vital Signs

Vital signs measurements include heart rate, respiratory rate, temperature, systolic blood pressure, and diastolic blood pressure. Vital signs will be listed by subject.

7.5.5.2 12-Lead Electrocardiogram

ECG measurements include heart rate, PR interval, RR interval, QRS interval, QT interval, QTc intervals. The number and percentage of subjects with elevated QTcF values (≥ 450 msec, > 480 msec, and > 500 msec) at baseline and any time post baseline will be presented. In addition, the number and percentage of subjects with QTcF values that increase by > 30 msec and > 60 msec from baseline to any time post baseline will be presented. ECG data will also be listed by subject.

7.5.5.3 Physical Examination

Results of the physical examination will be presented in subject data listings.

7.5.5.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). Prior medications include medications that were stopped

before the first dose of FLX475. Concomitant medications include medications that (1) started before the first dose of FLX475 and are continuing at the time of the first dose of FLX475, or (2) started on or after the date of the first dose of FLX475 up to 30 days after the subject's final dose. All medications will be presented in subject data listings.

7.6 Determination of Sample Size

The sample size of 20 subjects is considered adequate on clinical grounds to judge the safety of the combination therapy and obtain an initial estimate of its clinical efficacy.

The sample size of 6 subjects for the safety run-in portion is considered adequate to make an initial assessment of the safety of the combination therapy prior to enrolling a full 20-subject cohort.

7.7 Changes in the Conduct of the Study or Planned Analyses

The analyses outlined in this SAP include deviations from the protocol as outlined below.

- Efficacy analyses will not be summarized due to early discontinuation of the study and a limited amount of available efficacy data.

8 REFERENCE LIST

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

Hollander M, Wolfe DA. Nonparametric statistical methods. John Wiley & Sons, Inc. 1973.

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. John Wiley & Sons, Inc. 1980.

Long, G., Mortier, L., Schachter, J., Middleton, M., Neyns, B., Sznol, M., Zhou, H., Ebbinghaus, S., Ibrahim, N., Arance, A., Ribas, A., Blank, C. and Robert, C., 2017. Society for Melanoma Research 2016 Congress. Pigment Cell & Melanoma Research, 30(1), pp.76- 156