Protocol Number: 0103-020

Official Title: A Phase 1/2 Study of HDAC Inhibitor, Mocetinostat, in Combination With PD-L1 Inhibitor, Durvalumab, in Advanced or Metastatic Solid Tumors and Non-Small Cell Lung Cancer

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Statistical Analysis Plan

Sponsor:	Mirati Therapeutics, Inc.
Protocol No:	0103-020
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Title:	A Phase 1/2 Study of HDAC Inhibitor, Mocetinostat, in Combination With PD-L1 Inhibitor, Durvalumab in Advanced or Metastatic Solid Tumors and Non-Small Cell Lung Cancer
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1.0 Approvals

Sponsor	
Sponsor Name:	Mirati Therapeutics, Inc.
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2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Mirati Therapeutics, Inc. Protocol 0103-020.

3.0 Scope

This plan is a living document that supplements the study protocol for statistical analyses related aspects.

The SAP outlines the following:

- Study objectives and endpoints
- Study design
- Analysis populations
- Endpoint and variable definitions
- Data handling
- Data review
- Statistical methods

Deviations from the statistical analysis plan will be described in the Clinical Study Report (CSR).

4.0 Introduction

This SAP describes the statistical methods to be used during the analysis and reporting of data collected under Mirati Therapeutics, Inc. Protocol 0103-020.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 10 May 2017 and CRF dated 06SEP2016. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The SAP is to be developed in two stages. An initial SAP, known as SAP1, is finalized based on the current protocol and CRF, so that programming may be created. Changes following approval of SAP1 will be tracked in the SAP Change Log.A final version of the SAP, known as SAP2, will be issued prior to database lock.

Each version of the SAP requires approval by the project manager and the sponsor.

5.0 Study Objectives and Endpoints

5.1 Objectives

5.1.1 Primary Objectives

- To determine the recommended Phase 2 dose (RP2D) of mocetinostat administered in combination with full dose durvalumab,
- To evaluate the clinical activity of mocetinostat in combination with durvalumab in cohorts of patients with non-small cell lung cancer (NSCLC) having differing tumor expression of programmed cell death ligand 1 (PD-L1) or prior tumor responsiveness to treatment with checkpoint inhibitors.

5.1.2 Secondary Objectives

- To evaluate the safety and tolerability of mocetinostat in combination with durvalumab in the selected population,

- To evaluate secondary efficacy endpoints with mocetinostat in combination with durvalumab in the selected population,
- To evaluate mocetinostat and durvalumab pharmacokinetics (PK) [PK analysis will be covered by a separate analysis plan],
- To evaluate the incidence of anti-drug antibodies (ADA) to durvalumab,
- To evaluate the effect of mocetinostat during the Lead-In Period on tumor cell PD-L1 expression.

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

- Incidence of dose limiting toxicities (DLTs) occurring during the first 28-day cycle of combination treatment.
- Objective response rate (ORR) defined by RECIST 1.1.

5.2.2 Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events and laboratory abnormalities.
- Secondary efficacy endpoints:
    - Duration of response (DR)
    - Clinical benefit rate (CBR)
    - Progression free survival (PFS)
    - 1-year survival rate; and
    - Overall survival (OS).
- Blood plasma MGCD0103 and MED14736 concentrations.
- ADA detected in blood.
- Tumor PD-L1 expression.

[redacted]

[redacted]

6.0 Study Design

This is an open-label Phase 1/2 evaluation of mocetinostat in combination with durvalumab. The Phase 1 segment will define the RP2D of mocetinostat to be used in combination with full dose regimen of durvalumab; eligible patients will have an advanced solid tumor disease that is not amendable to curative treatment. The Phase 2 segment will evaluate the clinical activity of mocetinostat in combination with durvalumab, as assessed by ORR in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, in patients with locally advanced, unresectable or metastatic NSCLC who have previously received at least one platinum-containing doublet chemotherapy regimen for advanced disease. Patients who have previously received treatment with checkpoint inhibitors may be enrolled in the Phase 1 assessment and will be enrolled into dedicated cohorts in the Phase 2 assessment. Secondary objectives include secondary efficacy endpoints, PK, incidences of ADA and change in tumor PD-L1 expression. [redacted] The schedule of assessments to be performed in the study is presented in Table 1. Triplicate electrocardiogram (ECG) assessments, PK, and ADA collection time points are presented in Table 2.

The treatment regimen to be evaluated in this study includes a 7-Day Lead-In Period of mocetinostat single agent administered three times weekly (TIW; e.g., Monday, Wednesday and Friday) followed by administration of the combination regimen with durvalumab. The RP2D dose of mocetinostat will be established in successive dose escalation cohorts in the Phase 1 portion of the study and utilized in the Phase 2 portion of the study. The dose and regimen of durvalumab to be used throughout the study is 1500 mg on Day 1 of each 28-day cycle (i.e., Q4W).

Table 1: Schedule of Assessments

The Schedule of Assessments provides an overview of the protocol visits and procedures. Refer to Section **Error! Reference source not found.** for detailed information on each assessment. Additional, unplanned assessments should be performed as clinically indicated, including for the purpose of fully evaluating adverse events.

	Screen/ Baseline	7-Day Mocetinostat Lead-In Period	Mocetinistat + Durvalumab					End of Treatment[15]	
			Cycle 1		Cycle 2 and 3		≥Cycle 4		
Assessments	**Within 28 days**	**Day 1**	**Day 1**	**Day 15 (± 2 days)**	**Day 1 (± 2 days)**	**Day 15 (± 2 days)**	**Day 1 (± 2 days)**	**End of Treatment/ Withdrawal**	**Post Treatment Follow Up**
Study Participation Informed Consent[1]	Before study specific assessments								
Tumor PD-L1 Expression Testing[2]	X		X					X	
Medical History, Disease History, Prior Therapy	X								
ECOG Performance Status	X								
Physical Exam[3]	X							X	
Abbreviated Physical Exam[3]		X	X	X	X	X	X		
Vital Signs[4]	X	X	X	X	X	X	X	X	
Pregnancy Test[5]	X	As clinically indicated							
Hematology[6,7]	X	X	X	X	X	X	X	X	

Assessments	Screen/ Baseline	7-Day Mocetinostat Lead-In Period	Mocetinistat + Durvalumab					End of Treatment[15]	
			Cycle 1		Cycle 2 and 3		≥Cycle 4		
	Within 28 days	Day 1	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Coagulation[6,7]	X	As clinically indicated							
Urinalysis[6,7]	X		X		X		X		
Serum Chemistry[6,7]	X	X	X	X	X	X	X	X	
Thyroid Function Test[6,7]	X		X		X		X		
Blood for Pharmcokinetics[8]		See **Error! Reference source not found.**							90 Days
Blood for Anti-Drug Antibody[9]		See **Error! Reference source not found.**							90 Days
Biopsy of tumor for Biomarker Studies[10]	X		X		X[10]			X	
Blood Samples for Biomarker Studies[11]	X	X	X	X[11]	[11]				
Single 12-Lead ECG[12]	X				Cycle 3		X	X	
Triplicate 12-Lead ECG[12]		X, See **Error! Reference source not found.**	X		Cycle 2				
Echocardiogram	X			X	X		X	X	

Assessments	Screen/ Baseline	7-Day Mocetinostat Lead-In Period	Mocetinistat + Durvalumab					End of Treatment[15]	
			Cycle 1		Cycle 2 and 3		≥Cycle 4		
	Within 28 days	Day 1	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Disease Evaluation[13]	X		Q 8 weeks Starting from Cycle 1, Day 1 until Week 49 (~1 year) and then Q 12 weeks						
Mocetinostat Dispensing and/or Reconciliation		X	X		X		X		
Durvalumab Administration			X		X		X		
Adverse Events[14] and Concomitant Medications	SAEs only	Throughout							SAEs only for 90 Days
Long Term Follow-up[16]									X

1 Study Participation Informed Consent: May be performed prior to 28 days before first dose of study treatment and must be completed prior to study specific assessments.

2 Tumor Testing for PD-L1 Expression: Required test for patients enrolling in Cohorts 1 and 2; encouraged for patients enrolling in Phase 1 or Phase 2 Cohorts 3 and 4. Biopsy may precede informed consent if performed as Standard of Care (SOC) or to assess eligibility for a different clinical trial. In Cohorts 1 and 2, the sample tested must have been collected following completion of the most recent systemic treatment regimen.

3 Physical Examinations: A complete physical examination required at Screening and End of Treatment only. Height will be recorded at screening only. All other evaluations will be symptom-directed, abbreviated evaluations.

4 Vital Signs: Weight, temperature, blood pressure, and pulse rate to be assessed prior to dosing as indicated. In addition, blood pressure and pulse rate will be assessed every 30 minutes (± 5 minutes) between the start and end of durvalumab infusions and, for the first infusion, for 1 hour post infusion. If

the Durvalumab infusion period lasts 60 minutes, the first BP and pulse assessment should be made 30 minutes into the infusion and 30 minutes later at the end. If the infusion period lasts longer than 60 minutes, BP and pulse assessment should continue to be made at 30-minute (± 5 minutes) intervals.

5 Pregnancy Test: If the patient is a woman of childbearing potential, negative serum or urine pregnancy test performed by the local laboratory at screening will be required. The informed consent process must include discussion of the risks associated with pregnancy and adequate contraception methods. Additional pregnancy testing may be necessary if required by local practices or regulations, or if potential pregnancy is suspected.

6 Selected Lead-In, Day 1 Assessments: Repeat assessment not required if screening assessment performed within 7 days before the first dose.

7 Safety Laboratory Assessments: Hematology, coagulation, chemistry and thyroid function evaluations (see Section **Error! Reference source not found.**) will be performed by local laboratories. For scheduling convenience, these assessments may be performed one day prior to the visit at the start of the 7-day Lead-in Period and Cycle 1 Day 1.

8 Pharmacokinetic Samples: Blood samples to be collected following ECGs and assessment of vital signs as scheduled in **Error! Reference source not found.**. In addition, in the event of a Serious Adverse Event (SAE), unscheduled PK blood samples should be drawn for each study treatment as soon as possible.

9 Anti-Drug Antibody Samples: Blood samples to be collected as scheduled in **Error! Reference source not found.**.

10 Tumor Biopsy for Biomarker Studies: Consent for serial sampling of tumor tissue (preferably the same lesion) is requested but is not mandatory for study entry. The tumor biopsy used to determine eligibility may be used for the baseline assessment. Four collection timepoints are scheduled: baseline, C1D1, C2D1, and EOT. Markers of interest in tumor tissue include PD-L1 expression, CD8+ tumor infiltrating lymphocytes (TILs), natural killer cells (NK-cells), T regulatory cells (Tregs), and myeloid derived suppressor cells (MDSCs). Tumor biopsy tissue samples will not be collected on subjects in the Phase 1 50 mg cohort, and are optional for subjects in all other cohorts.

11 Blood Samples for Biomarker Studies: Blood samples for biomarker studies will not be collected on subjects in the Phase 1 50 mg cohort, but will be required for subjects in all other cohorts. At the beginning of the study, sampling will be scheduled on Cycle 1 Day 15. During the study, emerging data may indicate that quality of information gained from the assessment should improve with increased duration of combination treatment If so, the sample may be moved to Cycle 2 Day 1 and communicated to Investigators by Administrative Letter. Markers of interest in circulation include circulating PD-L1, Tregs, MDSCs, NK-cells, flow cytometry for T- and B-cell including CD4, CD8 and Ki67, and selected cytokines including CD8A, GZMB, IFNγ, CXCL9, CXCL10, CXCL11, and TBX21.

12 ECGs: Single 12-lead ECGs are to be performed at screening and at points not accompanied by PK sampling, with the exception of C3D1, C4D1 and C7D1. On days when PK samples are being collected, the single ECG should be performed prior to the blood draw. Triplicate ECGs are to be performed to as noted in **Error! Reference source not found.**. Assessments will include an evaluation of rhythm, heart rate, and PR, QRS, QT, and QTc intervals (Fridericia's formula). Respiration rate should be recorded during each ECG assessment.

13 Disease Evaluations: To be performed at screening (28 day window allowed) and every 8 weeks (± 10 days window) from C1D1 for all other assessments except screening until Week 49 (~1 year) and then every 12 weeks. At screening/baseline, assessments are to include CT with contrast of the chest, abdomen and pelvis, as well as brain Magnetic Resonance Imaging (MRI) with and without gadolinium or Computed Tomography Scan (CT) with contrast, a whole body bone scan and evaluation of any superficial lesions. Subsequent disease assessments should include all sites of disease identified at baseline or suspected to have developed; bone scans may be performed at one-half the frequency of other radiology evaluations and should be performed during assessment for confirmation of disease response. For those sites that routinely use PET scans for assessment of bone lesions in lieu of skeletal scintigraphy, PET scans may be used on-study, with the same modality planned throughout the study for any given patient. More detailed guidance on exceptional circumstances is provided in the protocol.

14 Adverse Events: SAEs will be reported from the time of informed consent until 90 days after the last administration of mocetinostat or durvalumab. Adverse events will be reported from the first day of study treatment until at least 28 days after last dose of study drug, and until resolution or stabilization of acute AEs and/or ongoing SAEs. After the 90-day SAE observation period, post-treatment follow-up may be performed by remote contact (e.g., telephone call).

15 End of Treatment: Assessments that have been completed in the previous 4 weeks do not need to be repeated (8 or 12 weeks for tumor assessments in accordance with schedule).

16 Long Term Follow-up: Blood samples for MEDI4736 PK and ADA will be collected approximately 90 days after the last infusion of durvalumab. Survival status and subsequent therapies will be collected during long term follow-up every 2 months (±14 days) from the date the subject was discontinued from study treatment until death or lost to follow-up. Follow-up beyond 90 days after last treatment may be performed by telephone contact.

Table 2: Schedule of Triplicate ECGs, PK and ADA Assessments

Nominal Cycle Day	Mocetinostat [1]		Durvalumab [1,2]	
	Triplicate ECG [3]	PK Sample [5,6,7]	PK Sample [5,6]	ADA Sample [6]
Lead-In Day 1	Pre-[4] and post-dose (1 hour only)	Phase 1: Pre- and post-dose (1, 3 and 7 hour) Phase 2: Pre- and post-dose (1 hour)		
Cycle 1 Day 1 (Day 1, Week 1)	Pre- and post-dose (1 hour only)	Phase 1: Pre- and post-dose (1, 3 and 7 hour) Phase 2: Pre- and post-dose (1 hour)	Pre-dose and end-of-infusion	Pre-dose
Cycle 1 Day 15 (Day 15, Week 3)		Pre- and post-dose (1 hour)	Pre-mocetinostat dose	
Cycle 2 Day 1 (Day 29, Week 5)	Pre- and post-dose (1 hour)	Pre- and post-dose (1 hour)	Pre-dose	Pre-dose
Cycle 3 Day 1 (Day 57,Week 8)		Pre- and post-dose (1 hour)	Pre-dose	
Cycle 4 Day 1 (Day 85, Week 13)			Pre-dose and end-of-infusion	Pre-dose
Cycle 7 Day 1 (Day 169, Week 25)		Pre-dose	Pre-dose	Pre-dose
Long Term Follow-up			90-days after last dose	90-days after last dose

1. On days mocetinostat and durvalumab are both administered and scheduled for PK assessment, mocetinostat dosing and sampling should precede durvalumab dosing.
2. The typical durvalumab infusion duration is 1-hour. End-of-infusion samples are to be collected within 5 minutes from the contralateral arm.
3. ECGs should be taken in triplicate, with readings at least 2 minutes apart. QTc should be manually calculated using Fridericia's formula.
4. On Lead-In Day 1, two sets of triplicate ECGs should be done within 1 hour prior to dosing (e.g., at 20-30 minute intervals) to firmly establish the baseline. In general, ECGs should be performed prior (within -30 to -5 minutes) to the respective PK blood collection.
5. Scheduled vital signs and triplicate ECGs precede PK sample collection in all cases.
6. Pre-dose sample allowable window up to 30 minutes prior to dose in all cases.
7. Allowable windows for mocetinostat post-dose samples are plus or minus 30 minutes for 1 hour post-dose and plus or minus1 hour for 3 and 7 hour samples.

6.1 Phase 1 Portion of the Study

The dose escalation phase of the study will employ the modified toxicity probability interval (mTPI) method in decision making concerning mocetinostat dose escalation (Appendix 3).

The mocetinostat dose levels planned for evaluation include 50, 70, and 90 mg TIW, depending on safety observations. In addition, if necessary, dose de-escalation of mocetinostat to 40 mg TIW may be undertaken.

	Screen/ Baseline	7-Day Mocetinostat Lead-In Period	Mocetinistat + Durvalumab					End of Treatment[15]	
			Cycle 1		Cycle 2 and 3		≥Cycle 4		
Assessments	Within 28 days	Day 1	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Coagulation[6,7]	X	As clinically indicated							
Urinalysis[6,7]	X		X		X		X		
Liver Enzyme Panel[6,7]	X	X	X	X	X	X	X		
Serum Chemistry[6,7]	X	X	X	X	X	X	X	X	
Thyroid Function Test[6,7]	X		X		X		X		
Blood for Pharmcokinetics[8]		See Table 2							90 Days
Blood for Anti-Drug Antibody[9]		See Table 2							90 Days
Biopsy of tumor for Biomarker Studies[10]	X		X					X	
Blood Samples for Biomarker Studies[11]	X	X	X	X[11]	[11]				
Single 12-Lead ECG[12]	X				Cycle 3		X	X	
Triplicate 12-Lead ECG[12]		X, See Table 2	X		Cycle 2				
Echocardiogram	X			X	X		X	X	

6.1.1 Definition of Dose Limiting Toxicity

The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03 will be used throughout this study. The definition of DLT includes any of the following events considered to be causally related to treatment with mocetinostat in combination with durvalumab:

- Any grade 4 immune-related adverse event (irAE is defined in Section 8)
- Grade 3 or greater colitis
- Grade 3 or greater noninfectious pneumonitis irrespective of duration
- Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Grade 3 irAE (excluding colitis or pneumonitis) that:
    - Does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids, or
    - Does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × upper limit of normal (ULN) or total bilirubin > 5 × ULN
- Grade 3 or greater non-irAE, except for the exclusions listed below:

- Nausea, vomiting, anorexia, dehydration, or diarrhea that can be managed with typical medical interventions.

The definition of DLT excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.

Note that the DLT evaluation period does not include the 7 day run in of mocetinostat.

6.1.2 Dose Escalation Plan

The first cohort of patients to be enrolled will begin with the mocetinostat 7-Day Lead-In Period, receiving 50 mg on 3 days (e.g., Monday, Wednesday and Friday) and will continue into the combination regimen, with 50 mg mocetinostat administered TIW and 1500 mg durvalumab administered Q4W.

For a patient within a dose cohort to be considered evaluable for the dose-escalation decision, the patient must have either been on study for 1 full cycle and have received treatment with durvalumab and at least 9 of 12 scheduled mocetinostat doses (75%) in Cycle 1 or have experienced a DLT in Cycle 1.

Decision making rules for cohort expansion and dose escalation or de-escalation based on the experience of patients treat at a dose level are presented in Appendix 3.

To ensure sufficient patient experience at the dose selected as the RP2D, enrollment at any dose level under consideration may be expanded to include at least 6 patients.

6.1.3 Definition of Maximum Tolerated Dose

The maximum tolerated dose (MTD) is defined as the highest mocetinostat dose administered in the combination regimen associated with the decision to “stay with the current dose” as determined from the Dose-Finding Spreadsheet (Appendix 3) using the experience of at least 6 patients during the first 28-day treatment cycle.

6.1.4 Definition of Recommended Phase 2 Dose

The RP2D will be the highest dose of mocetinostat evaluated that is associated with:

- Sufficient safety/tolerability to anticipate that patients will typically be able to receive treatment with at least 75% of the intended dose intensity of mocetinostat and 100% dose intensity of durvalumab; and
- No observed ≥ Grade 3 or serious irAEs causally related to the combination regimen.

A dose level below the MTD may be selected as the RP2D.

6.2 Phase 2 Portion of the Study

The Phase 2 portion of the study will enroll patients with NSCLC into one of the following 4 population cohorts:

- Cohort 1 – Patients naïve to treatment with immunotherapy, having tumor with no/low PD-L1 expression
- Cohort 2 – Patients naïve to treatment with immunotherapy, having tumor with high PD-L1 expression
- Cohort 3 – Patients previously treated with an anti-PD-L1 or anti-programmed cell death 1 (PD-1) agent with clinical benefit response followed by progression of disease
- Cohort 4 – Patients previously treated with an anti-PD-L1 or anti-PD-1 agent with progression of disease ≤ 16 weeks after initiation of treatment.

Tumor PD-L1 expression will be determined by the PD-L1 (SP263) CDx assay. No/low PD-L1 expression is defined as positivity <25% of tumor cells; high PD-L1 expression is defined as positivity ≥25% of tumor cells. Tumor samples used to establish PD-L1 expression for eligibility must have been collected after the most recent systemic therapy.

The sample sizes for the populations to be enrolled in the Phase 2 portion of the study are based on Predictive Probability Design, which allows for flexibility in the number of patients to be included at each stage in order to ensure that sufficient number of evaluable patients are available for decision to continue or to stop enrollment of additional patients.

- Cohorts 1, 3 and 4: Stage 1 of enrollment will include a minimum of 9 evaluable patients. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an Objective Response, 8 additional evaluable patients will be enrolled, for a total sample size of 17 evaluable patients. If at least 3 objective responses are observed, further investigation may be warranted.

- Cohort 2: Stage 1 of enrollment will include approximately 17 evaluable patients. With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective Responses, 27 additional evaluable patients will be enrolled, for a total sample size of 44 evaluable patients. If at least 18 Objective Responses are observed, further investigation may be warranted.

The exact stopping rules for all cohorts will be calculated based on the Predictive Probability Design, once the exact number of patients evaluable at Stage 1 is known. The aim is to get a minimum of 9 evaluable patients at Stage 1 for cohorts 1, 3 and 4 and about 17 evaluable patients at Stage 1 for cohort 2.
The populations included in Cohorts 3 and 4, who have had disease progression during treatment with a checkpoint inhibitor, represent a potential unmet medical need. For this reason, if results in Stage 2 of enrollment are of high interest, enrollment may be expanded to as many as 100 patients total in each cohort to narrow the 95% confidence interval (CI) around the ORR point estimate and more fully characterize the secondary endpoints in the population of interest.

In order to be part of the clinical activity evaluable population, the patient must have at least one on-study disease assessment or discontinue from treatment for PD prior to this assessment. Patients who

discontinue treatment prior to the first on-study disease assessment for an AE, toxicity, or withdraw consent are considered non-evaluable for disease assessment. These patients will not be part of the clinical activity evaluable population.

Disease response and progression as documented by the investigator in the CRF will be the basis for patient management and study expansion decision making. Unconfirmed objective responses recorded in the CRF may be used as an initial basis for expansion of study enrollment; however, follow-up evaluations on patients with unconfirmed responses must continue to support the decision to continue to the full number of patients to be included in the next stage. Central radiology review for disease response and progression may be added to the study during Stage 2. If this occurs, central review of all radiologic assessments performed in the study will be expected (including retrospective review of patients enrolled in Stage 1), and central radiology review for disease response will be the basis for the primary statistical analyses to estimate the ORR and its confidence interval, as well as the DR and PFS.

Study treatment will continue until disease progression, unacceptable AEs, patient refusal, or death.

6.3 Sample Size Considerations

6.3.1 Phase 1

Approximately 24 patients may be enrolled into the Phase 1 portion of the study. A precise sample size cannot be defined, as it is dependent on the number of dose escalations based on the mTPI method.

The mTPI method (Ji 2013) will be employed in decision making concerning dose escalation within each regimen investigated. The assumptions to be applied in establishing the mTPI methodology are:

- Each specific regimen exploration will include up to 30 patients
- The MTD is defined to have 0.25 probability of toxicity; and
- The acceptable variance around the MTD is ± 0.05 (i.e., the region of the MTD is 20% to 30% incidence of DLT).

6.3.2 Phase 2

Up to 261 patients may be enrolled into the Phase 2 portion of the study.

The 4-cohort Phase 2 portion uses sample sizes based on Predictive Probability Design (Lee-2008). ORR in accordance with RECIST 1.1 is the primary clinical benefit endpoint. In creating the statistical designs, the Type 1 error (α) is constrained to <0.05 and Power (1-β) is constrained to ≥0.90.

6.3.3 Statistical Design Applied to Phase 2 Cohorts 1, 3 and 4

The ORR using a PD-L1 inhibitor in the population with advanced NSCLC having no or low PD-L1 expression, or prior disease progression on a checkpoint inhibitor, is assumed to be 5% (p_0); thus this rate is considered uninteresting. The target ORR using mocetinostat in combination with durvalumab in this study is 30% (p_1). Stage 1 of enrollment will include a minimum of 9 evaluable patients per cohort. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an Objective Response, 8 additional evaluable patients will be enrolled, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed, further investigation may be warranted. If the true ORR is 5% (null hypothesis), the probability of early termination during the study is 0.63; the Type 1 error is equal to 0.0466 and the power is equal to 0.9045.

6.3.4 Statistical Design Applied to Phase 2 Cohort 2

The ORR using a PD-L1 inhibitor in the population with advanced NSCLC having high PD-L1 expression is assumed to be 27% (p_0); thus this rate is considered uninteresting. The target ORR using mocetinostat in combination with durvalumab in this study is 50% (p_1). Stage 1 of enrollment will include approximately 17 evaluable patients. With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective Responses, 27 additional evaluable patients will be enrolled, for a total sample size of 44 evaluable patients. If at least 18 Objective Responses are observed, further investigation may be warranted. If the true ORR is 27% (null hypothesis), the probability of early termination during the study is 0.50; the Type 1 error is equal to 0.0303 and the power is equal to 0.9018.

The exact stopping rules for all cohorts will be calculated based on the Predictive Probability Design, once the exact number of patients evaluable at Stage 1 is known. The aim is to get about 9 evaluable patients at Stage 1 for cohorts 1, 3 and 4 and about 17 evaluable patients at Stage 1 for cohort 2.

If Stage 2 results in Cohorts 3 and 4 are of high interest for efficacy (as decided by the sponsor), enrollment may be expanded to as many as 100 patients total in each cohort to narrow the 95% Confidence Interval (CI) around the ORR point estimate.

6.4 Randomization

There is no randomization for the study.

7.0 Analysis Populations

7.1 Enrolled Population

The enrolled population is defined as all patients who sign an informed consent for the study. Disposition summaries will be displayed using the enrolled population.

7.2 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population is defined as all patients who receive treatment with both mocetinostat and durvalumab on this study.

7.3 Clinical Activity Evaluable Population

In order to be considered eligible for the clinical activity evaluable population, the patient must have at least one on-study disease assessment or discontinue from treatment for PD. Patients who discontinue treatment prior to the first on-study disease assessment for an AE, toxicity, or withdraw consent are considered non-evaluable for disease assessment and will not be part of the clinical activity evaluable population.

This population will be used to present tumor responses as well as to make decision on the Predictive Probability design.

7.4 Safety Population

The safety population is defined as all patients who received at least 1 dose of either mocetinostat or durvalumab. The safety population will be used for all safety analyses.

7.5 DLT Evaluable Population

For a patient to be considered evaluable for dose-escalation decisions, or "DLT-evaluable," the patient must have either been on study for 1 full cycle and have received treatment with durvalumab and at least 9 of 12 scheduled mocetinostat doses (75%) in Cycle 1 or have experienced a DLT in Cycle 1.

Note that the DLT evaluation period does not include the 7 day run in of mocetinostat.

7.6 Molecular Marker Evaluable Population

The molecular marker evaluable population will consist of all patients who receive at least one dose of mocetinostat or durvalumab for whom PD-L1 expression results are available.

7.7 Pharmacokinetic Evaluable Population

The pharmacokinetic evaluable population will consist of all patients who had sufficient concentration-time data to permit calculation of PK parameters for mocetinostat or durvalumab. For patients who were noncompliant with respect to administration of mocetinostat, or for patients with incomplete data, a decision as to their inclusion in the analysis will be made on a case-by-case basis.

The PK analyses will be described in a PK analysis plan separate from this document.

7.8 Pharmacodynamic Evaluable Population

The pharmacodynamic evaluable population will consist of all patients who receive at least one dose of either mocetinostat or durvalumab for whom pharmacodynamic results are available.

7.9 Anti-Drug Antibody Evaluable Population

The ADA evaluable population will consist of all patients who receive at least one dose of either mocetinostat or durvalumab for whom ADA results are available.

8.0 Endpoint Definitions

8.1 Efficacy Variables

Disease assessments involving radiographic evaluations may be performed over the course of a few days. The date of response or progression (CR, PR, SD, PD or NE) will be recorded as the date of the last radiographic evaluation included in the series for that time point assessment. For central review (if this is done), the date of response or progression will be determined using the Date of Assessment associated with the applicable Time Point Assessment provided by the central review vendor; for the investigator assessment, the date will be determined using the latest Date of Assessment recorded among the radiologic modalities included for the applicable Time Point Assessment.

8.1.1 Objective Response Rate ORR)

Objective disease response will be categorized in accordance with RECIST v1.1. ORR is defined as the proportion of patients documented to have a confirmed CR or PR. If central review of disease response is undertaken, ORR as reported by the central radiology review laboratory will be used to calculate ORR and the exact binomial 95% CIs. ORR as reported by the investigator will be used in study expansion and decision making (PPD design).

8.1.2 Best Overall Response

Best Overall Response is defined as the best response among all overall responses (in the order complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD] and not evaluable [NE]) recorded from the start of study treatment until disease progression/ recurrence or end of the treatment, whichever comes first. Per RECIST version 1.1, the status of best overall response of PR or CR must be confirmed by repeat tumor assessment within no less than 4 weeks. If the status of CR or PR cannot be confirmed by repeat tumor assessment, the best overall response of unconfirmed CR and PR will be recorded as SD and NE. The status of best overall response of SD requires an on-study assessment after at least 35 days on treatment.

8.1.3 Clinical Benefit Rate (CBR)

CBR response will be categorized in accordance with RECIST v1.1. CBR is defined as the proportion of patients documented to have a confirmed CR or PR or SD documented during at least 2 on-study assessments and including at least 14 weeks on study (e.g., allowance for 2-week window around Week 17 assessment).

8.1.4 Duration of Response (DR)

DR is defined as the time in days from date of the first documentation of objective response (CR or PR) to the first documentation of objective progression of disease (PD) or to death due to any cause in the absence of documented PD (i.e., min [PD date, death date] – date of the first observation of response +1). Duration of response will only be calculated for the subgroup of patient achieving a Best Overall Response of CR or PR and will be presented for responses assessed by both central review and investigator's assessment.

Censoring rules will be applied to DR:

- Event time will be censored on the date of the last evaluable assessment documenting response for:
  - Patients on-study and progression-free at the time of an analysis;
  - Patients who have PD or death on study after ≥2 consecutive missed tumor assessments (i.e., >12 weeks + 14 days after the last on-study disease assessment);
  - Patients given alternative cancer treatment prior to PD or death on-study.
- Patients who die on-study after ≥2 consecutive missed tumor assessments (i.e., >12 weeks + 14 days after the last on-study disease assessment) will have their event time censored on the date of the last evaluable assessment documenting response.

8.1.5 Overall Survival (OS)

OS is defined as the time from first dose of study drug to the date of death due to any cause. OS (in months) is calculated as (date of death − date of first dose of study drug +1)/30.4. For patients who are continuing study at the time of an analysis, lost to follow-up or who withdraw consent, the OS endpoint will be censored on the last date that patients were known to be alive. The date last known to be alive is derived from the CRF and may include the latest Visit date for patients on-going study or the latest Date of Contact on the Long-Term Follow-Up/Survival Status page, whichever occurs latest. For patients with no follow-up after first dose of study drug, OS will be censored at the date of first dose.

8.1.6 Progression-Free Survival (PFS)

PFS is defined as the time from the first dose of study drug to the date of PD or death due to any cause, whichever occurs first. PFS (in months) will be calculated as (first event date – first dose date +1)/30.4.

Censoring rules will be applied to PFS:

- Patients lacking evaluation of disease after first study treatment will have their PFS time censored on the date of first dose with duration of 1 day unless they die within 2 tumor assessments of baseline, then they will be treated as an event with date of death as the event date.
- Patients with baseline or post-baseline assessments inadequate to apply RECIST criteria will have their event time censored on the date of the first dose of study drug.
- Event time will be censored on the date of the last evaluable assessment documenting absence of PD for:
  - Patients on-study and progression-free at the time of an analysis;
  - Patients who have PD or death on study after ≥2 consecutive missed tumor assessments (i.e., >12 weeks + 14 days after the last on-study disease assessment);
  - Patients given alternative cancer treatment prior to PD or death on-study.
- Patients who die on-study after ≥2 consecutive missed tumor assessments (i.e., >12 weeks + 14 days after the last on-study disease assessment) will have their event time censored on the date of the last evaluable assessment documenting absence of PD.

8.2 Study Drug Exposure Variables

Study Treatment Duration

Study treatment duration (days) is defined as (the last dose date – the first dose date +1) for mocetinostat and as (the last dose date – the first dose date +29) for durvalumab.

Days on Study Drug

Days on study drug is defined as the total number of days patient received drug, after subtracting time for interruptions or drug missed, that is, the latest Stop Date - the earliest Start Date captured on the Study Drug Administration CRF page – number of days with 0 mg dose +1 for mocetinostat and the latest Stop Date - the earliest Start Date captured on the Study Drug Administration CRF page – number of days with 0 mg dose +29 for durvalumab.

Cumulative Dose Received

For durvalumab, cumulative dose received (mg) is defined as the total amount of durvalumab a patient receives during the study, that is, the sum of dose administered as recorded on the Durvalumab Administration CRF form where dose administered equals 1500 when the planned dose was administered and is equal to the result of “If No, Dose Other Specify” question if the planned dose was not administered.

For mocetinostat, cumulative dose received (mg) is defined as the total amount of mocetinostat a patient receives during the study, that is, Sum of [(Stop date – Start date + 1) * Dose administered * Number of doses during this period of time] as recorded on the Mocetinostat Administration CRF form.

Cycles Started

A patient is considered to have started a cycle if they received at least one dose in that cycle, per the Study Drug Administration CRF page.

Dose Intensity

Absolute Dose intensity (mg/day) is calculated as cumulative dose received (mg) / Treatment duration (days).

Relative dose intensity is calculated as the cumulative dose received (mg) / initial planned cumulative dose (mg). Initial planned cumulative dose is calculated as the starting dose (day 1 cycle 1) multiplied by the study treatment duration.

Compliance is calculated as cumulative dose received (mg) / cumulative planned dose (mg, including dose decreased and interruptions as per physician's decision).

8.3 Safety Variables

Adverse events and laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

8.3.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 15.1 or higher).

Baseline Signs and Symptoms

- Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present on Day 1 of study drug dosing are recorded in the CRF as non-treatment emergent AEs, with actual start date, which will most often predate first dose. Baseline signs and symptoms will be reported separately from TEAEs.

Treatment-Emergent AEs (TEAEs)

- TEAEs are AEs that begin on Day 1 of study treatment or later during the on-study period. Baseline signs and symptoms that change attribution or severity during the on-study period are TEAEs. Any ongoing TEAEs that changes in attribution or severity is captured as a new AE.

Adverse Events of Special Interest (AESI)

AEs of special interest (AESI) for durvalumab based on observed safety event during durvalumab monotherapy and/or class effects for inhibitors of PD-L1 or PD-1 include:

- Colitis
- Pneumonitis
- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e., events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e., events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis – increased serum lipase, increased serum amylase).

Immune-related Adverse Event (irAE)

An irAE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology.

8.3.2 Vital Signs

Vital signs: systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, height and weight.

8.3.3 Clinical Laboratory Assessments

Clinical laboratory parameters to be collected routinely on-study are listed in Table 3 below.

Table 3: Laboratory Safety Parameters

Hematology Panel	**Blood Chemistry Panel**
Hemoglobin	Alanine aminotransferase (ALT)
Platelet count	Aspartate aminotransferase (AST)
White blood cell count (WBC)	Alkaline phosphatase
Neutrophil count	Lactate dehydrogenase (LDH)
Lymphocyte count	Total bilirubin (if Total bilirubin is ≥2xULN and no evidence of Gilbert's syndrome, then fractionate into direct and indirect bilirubin)
Basophil count	Gamma glutamyltransferase Screening, Day 1, and as clinically indicated
Monocyte count	Lipase
Eosinophil count	Amylase
	Creatinine
Coagulation	Blood urea nitrogen (BUN) or urea, depending on local practice
International normalized ratio (INR)	Uric acid
Prothrombin time (PT)	Total protein
Partial thromboplastin time (PTT)	Glucose (non-fasted)
	Albumin
Urinalysis (dip stick)	Calcium
Blood	Sodium
Glucose	Potassium
Protein	Chloride
	Magnesium
Thyroid Function Test	Bicarbonate [CO^2]
Thyroid-stimulating hormone (TSH)	
Free-T3 (if TSH abnormal)	
Free-T4 (if TSH abnormal)	

8.3.4 Electrocardiograms and echocardiograms

12-Lead electrocardiogram (ECG): rhythm, heart rate, PR, QRS, QT, RR and QTcF, the QT interval corrected for heart rate by the Fridericia's formula. Left ventricular ejection fraction (LVEF; %), pericardial effusion and hemodynamic compromise.

8.3.5 Prior and Concomitant Medications

Medications administered to study participants during the on-study period are captured on a log CRF page. Prior medications are defined as any medications with start and stop dates prior to the date of first dose of study drug. Concomitant medications are defined as medications administered to study participants on or after the date of first dose of study drug.

9.0 Data Handling

9.1 Missing Dates

The following rules will be applied to impute missing start and stop dates in appropriate data types (e.g., adverse events or concomitant medications).

Start Date

If the start date is completely missing (i.e., the day, month, and year are all unknown) the start date will be set to the date of first dose of study medication.

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the **first dose date**, then the day of the **first dose date** will be assigned to the missing day.
- If either the year is before the year of the **first dose date** or if both years are the same but the month is before the month of the **first dose date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **first dose date** or if both years are the same but the month is after the month of the **first dose date**, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the below procedure.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the **first dose date**, then the day and month of the **first dose date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **first dose date**, then January 1 will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **first dose date**, then January 01 will be assigned to the missing fields.

If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Stop Date

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the **last visit date**, then the day of the **last visit date** will be assigned to the missing day.
- If either the year is before the year of the **last visit date** or if both years are the same but the month is before the month of the **last visit date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **last visit date** or if both years are the same but the month is after the month of the **last visit date**, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the below procedure.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the **last visit date**, then the day and month of the **last visit date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **last visit date**, then January 1 will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **last visit date**, then January 01 will be assigned to the missing fields.

9.2 Protocol Deviations

Potential planned or unplanned protocol deviations noted during clinical monitoring will be documented by category (i.e., inclusion criteria, exclusion criteria, study drug, safety assessment, efficacy assessment, visit window, informed consent, prohibited medication, and other). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock. Important protocol deviations will be defined as those potentially impacting safety or efficacy assessments. Additional details of what will be considered important can be found in the Protocol Deviation Guidance document.

9.3 Study Day

Study day is defined relative to the date of the first dose of the study treatment. For assessments that occur after the first dose date, study day is calculated as (assessment date – the first dose date + 1). For assessments that occur prior to the first dose date, study day will be calculated as (assessment date – the first dose date); there is no Study Day 0.

Study Treatment

In this study, the study treatment refers to mocetinostat and/or durvalumab.

10.0 Interim Analyses

Tumor assessment is planned as per the Predictive Probability Design, after a first stage of enrollment, to decide whether or not a cohort should be stopped for lack of tumor response as detailed in Section 6.2.

11.0 Data Review

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to PRA Data Management.

Review of a pre-freeze TFL run on clean patients and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFLs will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve database lock.

12.0 Statistical Methods

All data collected during this study will be displayed in data listings, unless otherwise specified. Data listings will be sorted by dose level and patient identifier (regardless of phase) for safety listings and by

phase, dose level/cohort, and patient identifier for efficacy. Screen failures will be excluded from all tables and listings. In addition, listings will include all relevant derived variables.

Descriptive statistics (mean, median, standard deviations [STD], minimum and maximum values) for continuous variables will be presented. Mean and median will be presented to 1 decimal more than original data. STD will be presented to 2 decimals more than original data. Minimum and maximum will match the decimal points in the original data. For categorical variables, summary measures will include the frequency and percentage (with 1 decimal place) of patients in each category.

The summary tables will be presented by dose level (both phases combined) for safety and by phase and dose level/cohort for efficacy.

Unless otherwise noted, missing data will not be imputed or carried forward.

All data summaries and tabulations will be prepared with SAS® Version 9.4 or higher.

12.1 Patient Disposition

The number and percentage of patients enrolled and treated in the study will be presented, together with the number and percentage of patients who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal and the number and percentage of patients who discontinued mocetinostat and durvalumab with the corresponding reasons. will be reported by category for each phase and dose level/cohort, as well as overall within each phase. Additionally the number of patients in the mITT, Clinical activity evaluable, Safety, and DLT Evaluable populations will be presented.

12.2 Important Protocol Deviations

Important protocol deviations (see definition in Section 9.2) for patients in the Enrolled Population will be reported by category for each study arm. Important protocol deviations will be listed.

12.3 Treatments

12.3.1 Extent of Study Treatment Exposure

Exposure to treatment will be summarized by dose level for the Safety population separately for mocetinostat and durvalumab. Descriptive statistics will be provided for the duration of exposure (weeks), the total number of cycles started, number of doses received, cumulative dose received (mg) and dose intensity (mg/week).

Number and percentage of patients with at least 1 dose reduced (only for mocetinostat), at least 1 dose interrupted and reasons for dose reduction and interruption will be presented separately for mocetinostat and durvalumab.

Information regarding patients' dosing regimens will be listed separately for mocetinostat and durvalumab.

12.3.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) Drug Enhanced (version: March 2016).

Prior and concomitant medications will be tabulated separately for the Enrolled population by dose level Anatomical Therapeutic Chemical Classification and preferred drug name using counts and percentages. The number and percentage of patients using at least one medication within each dose level will also be displayed. See Section 8.3.5 for the definition of concomitant medications.

Prior and concomitant medications will be included in a patient data listing.

12.4 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized descriptively by phase and by dose level/cohort and overall within each phase for the Safety population. For continuous variables, descriptive statistics will include the mean, STD (or standard error), median, range, and interquartile range. For categorical variables, descriptive statistics will include the number and percent.

Demographic variables to be summarized include age (years), gender, reproductive status for female, ethnicity, race, weight (kg), height (m), smoking history and Eastern Cooperative Oncology Group (ECOG) status.

Medical history will be tabulated by system organ class (SOC) and preferred term (PT) using counts and percentages for the Safety population.

Primary Disease history will be tabulated for the Safety population and include the summary statistics (count and percentage) for Histology (Adenocarcinoma, squamous Cell Carcinoma, Large Cell Carcinoma and Other) and Current Stage (Locally Advanced, Metastatic).

Prior Primary Disease Treatment (Systemic therapy, radiotherapy and surgery) will be tabulated for the Safety population and include the summary statistics (count and percentage) for the following:

- Prior Systemic therapy - Platinum agent received (Cisplatin, Carboplatin, Other), Regimen (Neo-Adjuvant or Adjuvant, Advanced Disease Treatment Regimen, Other), Prior checkpoint inhibitor use (Nivolumab, Pembrolizumab, Durvalumab, Other)
- Prior radiotherapy – Type (Adjuvant, Palliative))
- Prior surgery – Location (Lung, Liver, Lymph Node, Adrenal, Brain, Other)

Demographic, medical history, primary disease history, and prior primary disease treatment data will be listed by patient.

12.5 Efficacy Analyses

12.5.1 ORR, Best Overall Response and CBR

Descriptive statistics (frequency and percentage) for ORR, CBR and of best overall response (CR, PR, SD, PD) based on the Response Assessments by the Investigator and the exact 95% Clopper-Pearson confidence interval (SAS® PROC FREQ) of the response rate will be presented by phase and by dose level/cohort and overall within each phase. An exact test (SAS® PROC FREQ) for single proportion (two-sided α=5%) will be performed to test H_0: ORR ≤5% against H_1: ORR >5% in cohorts 1, 3, and 4 and to test H_0: ORR ≤27% against H_1: ORR >27% in cohort 2, for phase 2 of the study. Patients who cannot be assessed for response will be counted as non-responders. Descriptive statistics (frequency and percentage) for CR and PR rate will be presented by phase, dose level/cohort, and overall within each phase. In addition, exact binomial 95% CIs for the percentage will be displayed for CR and PR rate, respectively.

The primary analyses will be conducted in the clinical activity evaluable population. Supportive analyses will be presented in the mITT population.

12.5.2 Time-to-event Variables

Time-to-event variables, DR, PFS, and OS, will be summarized by phase and by dose level/cohort and overall within each phase, descriptively using the Kaplan-Meier estimate (SAS® PROC LIFETEST). The median, 25th percentile, and 75th percentile of DR, PFS, and OS and their two sided 95% CIs using the complementary log-log transformation method (Collett, 1994) will be calculated where appropriate. In addition, minimum and maximum will also be displayed. Kaplan-Meier plots will be provided for DR, PFS, and OS.

DR, PFS, and CBR will be based on the Response Assessments by the Investigator. DR will be conducted in both the clinical activity evaluable and mITT populations. PFS and OS will be conducted in the mITT population.

12.5.3 ADA

The proportion of patients with ADA detected in the blood at any point throughout the study as well as at each time point will be summarized using counts and percentages in the ADA Evaluable population by phase, dose level/cohort and overall within each phase. The titer for the confirmed positive ADA samples will also be reported. If enough observations in ADA positive and negative groups are observed, AEs and ORR (per cohort and overall for phase 2 and overall for phase 1) will be evaluated per those subgroups.

12.5.4 PD-L1

For PD-L1 tumor expression, no/low PD-L1 expression is defined as positivity < 25% of tumor cells; high PD-L1 expression is defined as positivity ≥25% of tumor cells. The number of patients with no/low or high PD-L1 expression at baseline will be summarized using counts and percentages in the clinical activity evaluable and mITT populations by phase and dose level/cohort. ORR and OS (by phase) will be evaluated by those subgroups as well.

[redacted]

12.6 Safety Analyses

All safety analyses will be summarized by dose level, regardless of phase and all doses combined, by phase, in the Safety population.

12.6.1 Adverse Events

A summary of TEAEs, including the number and percentage of DLTs, number and percentage of patients reporting at least one TEAE, the number and percentage of patients reporting at least one CTCAE Grade 3 or greater TEAE, the number and percentage of patients discontinuing due to a TEAE, the number and percentage of patients with at least one serious adverse event (SAE), number and percentage of patients with at least one SAE by CTCAE grade, number and percentage of patients with at least 1 mocetinostat related TEAE, number and percentage of patients with at least 1 durvalumab related TEAE, number and percentage of patients with at least 1 TEAE related to both durvalumab and mocetinostat, number and percentage of patients with at least 1 mocetinostat related SAE, number and percentage of patients with at least 1 durvalumab related SAE, number and percentage of patients with at least 1 SAE related to both durvalumab and mocetinostat, number and percentage of patients discontinuing mocetinostat due to a TEAE, number and percentage of patients discontinuing durvalumab due to a TEAE, number and percentage of patients discontinuing mocetinostat due to a TEAE related to mocetinostat, number and percentage of patients discontinuing durvalumab due to a TEAE related to durvalumab, and the number and percentage of deaths will be presented. TEAEs are those that first occur or increase in severity or relationship to study treatment after the first dose of study treatment and not more than 30 days after the last dose of study treatment. In reality, all adverse events that change in severity or relationship to study treatment are assigned a new start date and captured as a new record. All AEs will be coded according to the MedDRA Version 19.0 dictionary by SOC, PT, and severity grade using NCI CTCAE Version 4.03.

A breakdown of the number and percentage of patients reporting each adverse event categorized by SOC and PT will be presented. Note that counting will be by patient not event and patients are only counted once within each SOC or PT. Similar summaries for CTCAE Grade ≥ 3 TEAEs, mocetinostat-related TEAEs, durvalumab-related TEAEs, CTCAE Grade ≥ 3 mocetinostat-related TEAEs, and CTCAE Grade ≥ 3 durvalumab-related TEAEs will be presented.

A further summary of the number and percentage of patients reporting each adverse event in at least 10% of patients will be categorized by PT in descending order of frequency.

A summary of events reported categorized by maximum CTCAE grade will also be provided. Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT. Similar summaries for mocetinostat-related TEAEs and durvalumab-related TEAES will be presented.

Separate summaries of adverse events leading to mocetinostat and durvalumab discontinuation will be provided, grouped by SOC and PT. Separate listings of patients who discontinue mocetinostat and durvalumab due to a TEAE will be presented. Further summaries of mocetinostat-related TEAEs leading to mocetinostat discontinuation and durvalumab-related TEAEs leading to durvalumab discontinuation will be provided.

Pericardial adverse events will be categorized by PT in descending order of frequency. Patients with pericardial events will be listed.

All AEs (including non-treatment-emergent events) recorded on the CRF will be listed.

12.6.2 Deaths and Serious Adverse Events

TEAEs that lead to death will be summarized by SOC and PT. A listing of patients who die will be presented. SAEs will be summarized by SOC and PT. A listing of patients who experience a SAE will also be presented.

Separate summaries for SAEs related to mocetinostat and related to durvalumab grouped by SOC and PT will be presented.

12.6.3 Laboratory Data

All laboratory data will be summarized in International System (SI) units. The conversion factors from conventional to SI units will be documented in the Local Lab Conventions document for this study. In general, laboratory data will be presented by visit. Values at unscheduled visits will be included in the summary of maximum for all cycles and minimum for all cycles, which will present the largest and smallest values observed for each patient post-baseline for each test.

Selected parameters will be presented in shift tables of baseline against worst grade test result. The shift from baseline to worst post baseline (including unscheduled visit) NCI CTCAE Version 4.03 grade will be presented by dosing group and overall for albumin (albumin increased), AST (AST increased), ALT (ALT increased), bilirubin (bilirubin increased), creatinine (creatinine increased), hemoglobin (anemia), neutrophils (neutrophil count decreased), platelets (platelet count decreased), sodium (hyponatremia and hypernatremia), potassium (hypokalemia and hyperkalemia), calcium (hypocalcemia and hypercalcemia), phosphate (hypophosphatemia), and uric acid (hyperuricemia).

For sodium, potassium, and calcium, separate grading criteria exist depending whether the analyte is high or low. For the purpose of shift tables, all low values will be included in the Grade 0 group in the shift tables for high values, and vice versa (all high values should be included in the Grade 0 group in the shift tables for low values.

Subjects with at least 1 on-study measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present.

Clinical laboratory results will be listed by subject. Laboratory values that meet Grade 3 or 4 criteria according to NCI CTCAE Version 4.03 will also be listed separately.

12.6.4 Hematology

Hematology parameters include hemoglobin, platelet count, white blood cell (WBC) count, lymphocytes, monocytes, neutrophils, eosinophils, and basophils. The coagulation parameters include prothrombin time (PT), partial thromboplastin time (PTT) and international normalization ratio (INR).

Descriptive statistics will be provided for each test result and for change from baseline by cycle. Multiple measurements taken during the visit for a patient will be represented by the most severe value for each hematology test. The most severe value will be determined first by the value closest to the upper or lower limit of the normal limits (dependent on which direction is considered severe) if the value is within the normal limits. If the value is outside the normal limits, the value furthest from the upper or lower limit will be selected (dependent on which direction is considered severe). In the event that this algorithm does not allow for determining the most severe (e.g., a tie, etc.) the first chronological value will be selected. Low values are considered the most severe for all hematology parameters. Shift tables tables (for hemoglobin (anemia), neutrophils (neutrophil count decreased), platelets (platelet count decreased)), summarizing the shift from baseline grade to each post-baseline visit, maximum post-baseline CTCAE grade including unscheduled visits, and last assessment on study will be presented. Patients who develop a ≥ Grade 3 toxicity will be listed.

12.6.5 Chemistry

Serum chemistry parameters include ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, indirect bilirubin, gamma glutamyl transferase (GGT), lipase, amylase, creatinine, uric acid, blood urea nitrogen (BUN), total protein, glucose (non-fasted), albumin, sodium, potassium, chloride, total calcium, magnesium, and bicarbonate.

Descriptive statistics will be provided for each test result and for change from baseline by cycle. Multiple measurements taken during the visit for a patient will be represented by the most severe value as noted in Section 12.6.3. For all chemistry analytes, the most severe value is the highest value, with the exception of albumin, chloride, and bicarbonate. The most severe could be in either direction for glucose, potassium, sodium, and calcium. For these analytes, if within the normal limits, then the value closest to the normal limit (either direction) will be selected. If outside the normal limits, then the value most distant from the normal limit (either direction) will be used. Shift tables (for AST (AST increased), ALT (ALT increased), creatinine (creatinine increased), sodium (hyponatremia and hypernatremia), potassium (hypokalemia and hyperkalemia), calcium (hypocalcemia and hypercalcemia), phosphate (hypophosphatemia), and uric acid (hyperuricemia), summarizing the shift from baseline grade to each post-baseline visit, maximum post-baseline CTCAE grade including unscheduled visits, and last assessment on study will be presented. Patients who develop a ≥ Grade 3 toxicity will be listed.

12.6.6 Urinalysis

Urinalysis results for the parameters blood, protein, and glucose will be listed.

12.6.7 Thyroid

Results will be listed for thyroid-stimulating hormone (TSH), and if TSH is abnormal, then Free-T3 and Free-T4 will also be listed.

12.6.8 CTCAE Coding of Laboratory Data

Where laboratory values are categorized into NCI CTCAE v4.03 grades, the categories are defined according to the criteria available on the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Note that grades are applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not considered. For example, Grade 4 hyperglycemia will be assigned based solely on the value of the glucose measurement, and acidosis will not be considered. Where categories are only distinguished by clinical signs or symptoms, the lowest of the possible grades will be assigned.

NCI CTCAE grades will be applied for the following lab parameters:

- Hematology: hemoglobin, white blood cell (WBC), lymphocyte, neutrophils, and platelets.
- Chemistry: ALT, albumin, Alkaline, phosphatase, AST, total bilirubin, calcium, creatinine, phosphate, magnesium, potassium, sodium, uric acid.

Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as “Grade 0,” which is defined as normal.

12.6.9 Vital Signs

Clinically significant findings noted during screening will be reflected on the medical history CRF, while those noted during study treatment will be collected on the AE CRFs. The following vital signs will be summarized: pulse rate (beats/min), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), body temperature (C), and weight (kg). Vital signs and change from baseline will be summarized in two ways. First, all vital signs and change from baseline through the last Cycle will be summarized. In these tables, baseline will generally be the Cycle 1 Day 1 measurement for all comparisons. This will include a summary of the maximum and minimum values observed while the patient was on treatment and change from baseline to that observed value

All vital signs including baseline ECOG will be listed.

12.6.10 Physical Examinations, ECGs, and Other Observations Related to Safety

12.6.11 Physical Examination

Complete physical examinations will be conducted during screening and at the End of Treatment visit. Abbreviated physical examinations will be performed on Day 1 of the 7-day Mocetinostat Lead-in Period, Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of the remaining cycles. Any new abnormal physical exam findings will be collected as AEs. Physical Examination data will be listed for the Safety population.

12.6.12 Electrocardiogram

A summary of ECG parameters including heart rate (beats/min), PR (msec), QRS (msec), QT interval (msec), QTcF (msec), and RR interval (msec) and change from baseline will be presented for each planned visit. A summary of change from baseline to worst grade for ICH E14 categories will also be presented. In addition, listings and summaries will be generated for patients with QTcF increased to value >480 and <500 msec, and value >500 msec, and patients with change-from-baseline QTcF increased by 30 to <60 msec, and by >60 msec.
A separate listing of the ECG results along with the overall interpretation will be presented.

12.6.13 Echocardiogram

A summary of the left ventricular ejection fraction (LVEF; %) and change from baseline will be presented for each planned visit. Additionally, the number of patients with pericardial effusion assessment along with the result of the assessment and the hemodynamic compromise will be summarized

12.6.14 Pregnancy Test

For patients of childbearing potential, a serum or urine pregnancy test will be performed at screening. Pregnancy tests will also be done whenever pregnancy is suspected during the study. Additional pregnancy testing may be necessary if required by local practices or regulations. Pregnancy testing data will be listed by dose level for the Safety population.

12.6.15 Long Term Follow-up

Long term follow-up/survival data will be listed for the safety population. Additionally, all follow-up anti-cancer therapy will be listed.

13.0 Validation

PRA seeks to ensure the quality of the results provided for the study in the form of TFLs, and the derived datasets used in their creation, through the following processes:

The entire set of TFLs will be checked for completeness and consistency prior to its delivery to the client by the lead analysis programmer, the lead statistician, and a senior level statistician, or above, who is not a member of the project team.

The PRA validation process will be repeated any time TFLs are redelivered using different data. Execution of this validation process will be documented through the study Table of Programs that will be provided to Mirati at study conclusion.

14.0 References

Collet, D. (1994), Modeling Survival Data in Medical Research, London: Chapman & Hall.

Ji Y and Wang SJ. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3 + 3 Design For Practical Phase I Trials. *J Clin Oncol*, 31:1785-1791, 2013.

Appendix 1 Glossary of Abbreviations

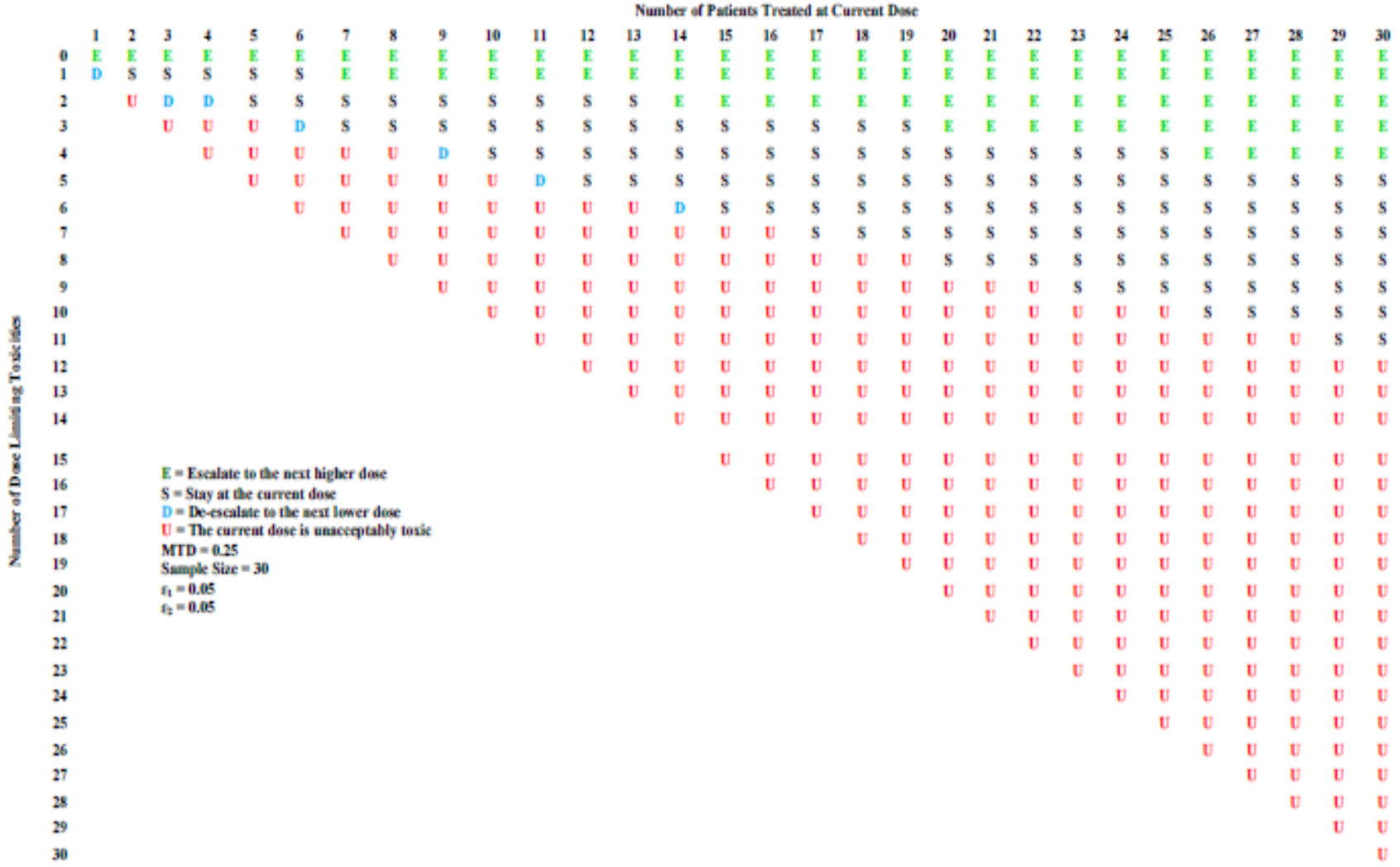
Glossary of Abbreviations:	
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
C	Celsius
CBR	Clinical Benefit Rate
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GGT	Gamma Glutamyl Transferase
HDAC	Histone Deacetylases
irAE	Immune-related Adverse Event
INR	Internal Normalization Ratio
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
mITT	Modified Intent-to-treat
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
NCI	National Cancer Institute
NE	Not Evaluable
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease

PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression-free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SLD	Sum of Lonest Diameter
SD	Stable Disease
SI	International System
SOC	System Organ Class
STD	Standard Deviation
TEAE	Treatment-emergent Adverse Event
TFL	Tables, Figures, and Listings
TSH	Thyroid-stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

Appendix 2 Tables, Figures, Listings, and Supportive SAS Output Appendices

The TFL shells for this study are provided in a separate document titled “Mirati 0103-020 SAP TLFs Shells Version 0.1.docm”.

Appendix 3 Dose-Finding Spreadsheet of the Modified Toxicity Probability Interval (mTPI) Method



Appendix 4 Programming Specifications for Baseline Characteristics and Safety Variables

Patient Disposition

- **Enrolled Patients**

An enrolled patient is one with response to "Was the patient enrolled into the study?" on the Eligibility Criteria and Enrollment CRF page is Yes.

- **On Treatment**

A patient will be considered on treatment if he/she has had at least one dose of the study treatment and is not captured on either the End of Treatment Mocetinostat or the End of Treatment Durvalumab CRF pages.

- **Discontinued Treatment**

A patient will be considered to have discontinued mocetinostat or durvalumab if he/she is captured on the End of Treatment Mocetinostat or the End of Treatment Durvalumab CRF page, respectively.

- **In Long Term Follow Up**

A patient will be considered to be in long term follow up if the response to the question "Will the patient be followed for Follow-up?" on either the End of Treatment Mocetinostat or the End of Treatment Durvalumab CRF pages is "Yes."

- **On Study**

A patient will be considered on study if the End of Study CRF page has NOT been completed indicating primary reason for ending study.

- **Discontinued Study**

A patient will be considered to have discontinued from the study when an End of Study CRF page is completed indicating primary reason for ending study.

Age

The following SAS® code will be used to calculate patient age (years):
Age = floor ([intck{'month', birth date, Informed Consent Date} - {day(Informed Consent date) < day(birth date)}] / 12), where intck is a SAS® function counting integer days. If the day and month of a patient's date of birth are not collected due to some countries' Privacy Laws, age will be calculated using the year of informed consent/assent minus year of birth.

Baseline, Change from Baseline

Baseline is defined as the most recent measurement prior to the first dose of study treatment.
Change from baseline is defined as (value at post baseline visit – value at baseline).
Percent change from baseline is defined as [(value at post baseline visit – value at baseline) / value at baseline] * 100%.

Postbaseline values for tabulations generally will exclude unscheduled visit values, but unscheduled visit values will be included in listings.

QTcF

QT corrected for heart rate by Fridericia's correction, i.e., $QTcF = QT / RR^{1/3}$.