STATISTICAL ANALYSIS PLAN

HBI-8000-302

A Phase 1b/2 Study to Assess the Safety and Efficacy of HBI-8000 in Combination with Nivolumab in Subjects with Advanced Solid Tumors Including Melanoma, Renal Cell Carcinoma (RCC) and Non-Small Cell Lung Cancer (NSCLC)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 01Apr2022) for Protocol HBI-8000-302.

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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			Removed reference to PK waterfall plots and Kaplan-Meier plots Changed ENR set to ICS

LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
$AUC_{(0-7)}$	Area under the curve from zero (predose) to 7 hours postdose.
$AUC_{(0-7)}/D$	Dose-normalized $AUC_{(0-7)}$
$AUC_{(0-7)}$ Ratio	Ratio of $AUC_{(0-7)}$ on Cycle 2 Day 1 : Cycle 1 Day 1
$AUC_{(0-24)}$	Area under the curve from zero (predose) to 24 hours postdose.
$AUC_{(0-24)}/D$	Dose-normalized $AUC_{(0-24)}$
BLQ	Below the limit of quantitation
BMI	Body mass index
BOR	Best overall response
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CBR	Clinical benefit rate
CI	Confidence interval
C_{max}	Maximum plasma drug concentration
C_{max}/D	Dose-normalized C_{max}
C_{max} Ratio	Ratio of C_{max} on Cycle 2 Day 1 : Cycle 1 Day 1
C_{pre}	Predose observed plasma concentration
C_{pre}/D	Dose-normalized C_{pre}
CQT	Concentration – QTc modeling
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation (percentage)
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration (U.S.)
HEENT	Head, eye, ear, nose, and throat
ICF	Informed consent form
ICS	Informed Consent Set
INR	International normalized ratio

IO	Immunotherapy
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ND	Not determined
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-L1	Programmed Death-Ligand 1
PDS	Pharmacodynamic Set
PHD	Pharmacodynamic
PFS	Progression-free survival
PKS	Pharmacokinetic Set
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial response
PT	Preferred term
PTI	Prothrombin time
QTcF	QT interval corrected by heart rate, using Fridericia's formula
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease
SMQ	Standardized MedDRA Query
SOC	System organ class
Std	Standard Deviation
TEAE	Treatment-emergent adverse event
t_{max}	Time to peak plasma drug concentration
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
T4	Thyroxine
ULN	Upper limit of normal
ULQ	Upper limit of quantification
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	WHO drug dictionary enhanced

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetics (PK), and pharmacodynamic (PHD) (Holter ECG) data for Protocol HBI-8000-302. It describes the data to be summarized and analysed, including specifics of the statistical analyses to be performed. The exploratory endpoint of histone acetylation in peripheral blood mononuclear cells is outside the scope of this document.

This statistical analysis plan (SAP) is based on HBI-8000-302 protocol version 6.0, dated 29 March 2021.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the safety and tolerability of HBI-8000 when combined with a standard dose and regimen of Nivolumab, to determine Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D) and to evaluate frequency and severity of toxicities of this combination treatment.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To explore the efficacy of study treatment as measured by Objective Response Rate (ORR), Disease Control Rate (DCR), Clinical Benefit Rate (CBR), Duration of Response (DoR), and Progression-Free Survival (PFS) in all subjects treated at RP2D
- To obtain PK of twice weekly HBI-8000 when administered in combination with Nivolumab administered once every two weeks per package insert dose (Appendix 9 in the Protocol) and administration (Phase 1b all sites)
- To obtain PK of twice weekly HBI-8000 when administered in combination with nivolumab administered (Phase 2 selected sites)
- To characterize the effect of HBI-8000 on the electrocardiogram (ECG) QT interval corrected for heart rate (QTc interval) (Phase 1b only)

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To investigate the kinetics and extent of histone acetylation in peripheral blood mononuclear cells (PBMC) at the RP2D of HBI-8000 (Phase 2 only)

- To explore potential biomarkers for disease response through sequential sampling of blood and /or tumor tissue in subjects consenting to correlative sub-studies at participating sites (Phase 2 only)

2.4. SAFETY OBJECTIVES

The safety objective is to monitor the safety of HBI-8000 when combined with a standard dose and regimen of Nivolumab in subjects with advanced solid tumors including Melanoma, Renal Cell Carcinoma (RCC) and Non-Small Cell Lung Cancer (NSCLC).

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multicenter, open label, Phase 1b/2 dose finding trial of HBI-8000 in combination with US Food and Drug Administration (FDA) approved dose of Nivolumab in Melanoma, RCC and NSCLC. In Phase 1b (Part 1), the safety of escalating dose levels of HBI-8000 in combination with Nivolumab will be assessed. In Phase 2 (Part 2), Original Protocol – Protocol Amendment 4 versions, preliminary efficacy of HBI-8000 at MTD and/or RP2D in combination with nivolumab will be explored in subjects with advanced cutaneous melanoma, and NSCLC (subjects with RCC will not be included in Phase 2). Under Protocol Amendment 5, only subjects with advanced cutaneous melanoma will be enrolled in Phase 2 (Part 2) to explore the preliminary efficacy of HBI-8000 at MTD and/or RP2D in combination with nivolumab. Under Protocol Amendment 6, only subjects with advanced cutaneous melanoma who have not been treated with programmed death-ligand 1 (PD-L1) inhibitor will be enrolled in Phase 2 (Part 2).

In Phase 1b (Part 1), dose escalation schema of HBI-8000 follows the conventional 3+3 design. The starting dose will be HBI-8000 20 mg twice a week. Dose escalation to 30 mg or 40 mg is determined by observation of dose limiting toxicity (DLT). At each dose level, a minimum of 3 subjects evaluable for DLT will be enrolled. If 0 of the initial 3, or no more than 1 in a total 6 subjects experienced DLT, escalation to next higher dose is allowed. The RP2D will be confirmed in at least 6 evaluable subjects to ensure that no more than 1 out of these 6 subjects experienced DLT. There will be a maximum of 18 subjects in the dose escalation phase.

In the Phase 2 (Part 2), which is the dose expansion cohort, HBI-8000 at RP2D in combination with Nivolumab will be evaluated in tumor-specific cohorts:

- Melanoma – up to 40 subjects who have not been treated with PD-L1 inhibitor, and 20 subjects previously treated with at least a PD-L1 inhibitor. With Protocol Amendment 6, only subjects with advanced cutaneous melanoma who have not been treated with PD-L1 inhibitor will be enrolled in Phase 2 (Part 2).

- NSCLC - up to 20 subjects who have not been treated with PD-L1 inhibitor, and 20 subjects previously treated with at least a PD-L1. With Protocol Amendment 5, subjects with NSCLC are no longer eligible for enrolment.

Preliminary efficacy will be explored for each tumor type in subjects enrolled in Phase 1b and Phase 2.

Study drug administration will be as follows:

- Each treatment cycle consists of 28 consecutive days.
- HBI-8000 will be administered orally approximately 30 minutes after a regular meal twice a week with 3-4 days between dosing.
- Nivolumab will be administered as follows:

  In Phase 1b, nivolumab (240 mg) will be administered according to Prescribing Information intravenously every two weeks. On Days 1 and 15 of each cycle (except for Cycle 1 Day 1), the subject will receive both HBI-8000 and nivolumab. In Phase 1b, on Cycle 1 Day 1, subjects will receive only HBI-8000 to allow for QTc study; on Cycle 1 Day 2, subjects will receive only nivolumab.

  During cohort expansion (Phase 2), nivolumab will be administered according to Prescribing Information in the package insert (Appendix 9 in the Protocol). Both HBI-8000 and nivolumab will be administered on Cycle 1 Day 1. However, on Cycle 1 Day 1, for subjects participating in the PK study, nivolumab will be administered after the last PK time point.
- Throughout the study (Phase 1b and Phase 2), PK of HBI-8000 will be obtained according to the PK sparse sampling schema described in the Table of Events (Appendix 1 in the Protocol) and Appendix 2 and 3 of the Protocol.
- In the Phase 1b portion of the trial only, to accommodate the QTc study of HBI-8000 in Cycle 1 Day 1, nivolumab will be administered on Days 2 and 15 of Cycle 1, subjects will receive nivolumab 240 mg by intravenous (IV) infusion over 60 minutes. For Cycle 2 and beyond, nivolumab will be administered on Days 1 and 15 of the Cycle.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Appendix 1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

A noncompartmental PK analysis and calculation of PK parameters has been added. The statistical assessment of the relationship between QTc and PK concentrations specified in Section 7.13.2 of the protocol will be carried out using data from the current study alone and will be reported in the clinical study report of the current study.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Data Safety and Monitoring Board (DSMB) meetings
- Final Analysis

Analysis for DSMB was a subset of the final analysis based on SAP Version 1.1.

4.1. Data Safety and Monitoring Board

This SAP will describe the methodology and presentation of results as they will be used for the DSMB. The DSMB Charter will specify the analyses and tables, listings and figures that will be provided to the DSMB members at each meeting.

4.2. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following HUYABIO International's Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets.

5. Analysis Sets

5.1. Informed Consent Set [ICS]

All subjects who signed the informed consent form (ICF).

5.2. Safety Set [SAF]

All subjects who have received at least 1 dose of HBI-8000. The safety set will be the primary set for evaluating treatment administration / compliance and safety in the study. Subjects will be classified according to the first dose of HBI-8000 into dose groups.

5.3. Full Analysis Set [FAS]

The full analysis set for efficacy consists of all subjects meeting all eligibility criteria who receive at least one dose of HBI-8000, and either have at least one post-baseline assessment of efficacy by imaging studies or discontinue study early due to clinical progressive disease (PD) in the absence of imaging study.

5.4. Per Protocol Set [PPS]

The per protocol set for efficacy consists of subjects meeting all eligible criteria, having received at least 2 cycles of HBI-8000 (any 2 cycles including those with drug interactions), with at least 1 imaging study to evaluate disease status after completing 2 cycles of treatment.

5.5. Pharmacokinetic Set [PKS]

All subjects who receive at least one dose of HBI-8000 and have at least one postdose blood sample providing evaluable PK data for HBI-8000. Subjects and/or data affected by protocol deviations or

events that could impact PK (such as within-subject change in dose, incorrect dose, emesis associated with dosing, meal not administered prior to HBI-8000 dosing, etc.) will be included in listings but excluded from the PKS.

The dataset associated with the PKS summarized in the clinical study report may be different from the dataset utilized for population PK analysis (reported separately).

5.6. PHARMACODYNAMIC SET [PDS]

All subjects who have Baseline Holter ECG measurements and at least one postdose Holter ECG measurement which are evaluable for PHD. Subjects and/or data affected by protocol deviations or events that impact PK (such as within-subject change in dose, incorrect dose, emesis associated with dosing, etc.) will be included in listings but excluded from the PDS.

5.7. DOSE LIMITING TOXICITY SET [DLTS]

All subjects who 1) receive ≥ 75% of the planned total amount (in mg) of HBI-8000 in the absence of treatment delays due to toxicities over the first 28 days or 2) experience DLT within the first two weeks after having received 100% of assigned dose of HBI-8000.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of HBI-8000 (where Day 1 is the day of the first dose of HBI-8000), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings. See Appendix 2 for handling of the partial or missing dates for adverse events and concomitant medications.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last measurement taken prior to reference start

date/time (including unscheduled assessments).

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will be included in listings.

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

Any PK windowing is described in Section 17.2.2. No other visit windowing will be performed for this study.

6.5. STATISTICAL TESTS

Not applicable.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

Baseline value is defined as the measurement obtained at the last assessment before first dose of HBI-8000, unless otherwise specified.

6.7. SOFTWARE VERSION

The software Phoenix® WinNonlin® Version 6.4, or higher (Certara, L.P., Princeton, New Jersey, USA) and/or SAS version 9.4 or higher will be used for calculation of PK parameters. All other analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Adjustments for covariates and factors are not applicable to this study.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers within the US.

7.3. MISSING DATA

All of the analyses will be based on the observed data with no imputation for the missing data with the exception of partial dates as described in Appendix 2. The handling of PK concentrations that are missing or below the limit of quantitation (BLQ) are described in Section 17.2.2.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not Applicable in this Phase 1b/2 study with one treatment arm.

7.5. EXAMINATION OF SUBGROUPS

Select analyses will be done for only those subjects with PK or Holter ECG assessments.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

Unless otherwise specified in the output template,

- All Phase 1b tables (including safety, disposition, demographic and baseline characteristics, medical history, disease history, etc.) will present overall subjects in the specified analysis set by HBI-8000 dose. No separate summaries by tumor type are needed.
- All tables of Phase 2 data or combined Phase 1b and Phase 2 data (including efficacy, safety, disposition, demographic and baseline characteristics, medical history, disease history, etc.) will be presented by tumor groups (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC) with all HBI-8000 doses combined.
- Listings will be presented by phase and tumor groups (Melanoma Immunotherapy (IO)-

naïve/treated, NSCLC IO-naïve/treated, RCC), and within each phase and tumor group sorted by HBI-8000 dose (20mg, 30 mg and 40mg), subject ID.

The TFL shells are presented in a separate document. Upon approval of the final SAP, some minor updates on the TFL shells (title, footnotes, and headings etc.) are allowed as long as the updates do not conflict with the contents in the SAP.

9. DISPOSITION AND WITHDRAWALS

All subjects who signed informed consent (IC Set) will be accounted for in this study.

The following subject sets and disposition will be summarized by frequency and percentage (%) if applicable:

- Informed Consent set (ICS)
- Dose Limiting Toxicity Set (DLTS) [For Phase 1b]
- Safety analysis set (SAF)
- Subjects who received nivolumab treatment
- Full analysis set (FAS)
- Per-protocol set (PPS)
- Subjects who received protocol required HBI-8000 and Nivolumab
- Subjects who discontinued HBI-8000 or Nivolumab prematurely
- Reasons for HBI-8000 or nivolumab discontinuation (adverse event, progression of the disease by response evaluation criteria in solid tumors (RECIST) 1.1, clinical progression, decision by investigator, subject request to withdraw informed consent, intercurrent illness, significant protocol deviations, subject noncompliance, subject is beginning another anti-cancer treatment protocol, pregnancy, death, or other as reported on the Disposition page of the electronic Case Report Form [eCRF])
- Subjects who completed the HBI-800 treatment per the protocol.
- Subjects who discontinued the study
- Reasons for discontinuation from study (subject decision, death, lost to follow-up, study terminated by sponsor, or other as reported on the End of Study Page of the eCRF)
- Pharmacokinetic Set (PKS) [Phase 1b only]
- Pharmacodynamic Set (PDS) [Phase 1b only]

Subject disposition and withdrawals after treatment will be presented with frequency and percentages.

Percentages will be calculated based on the Safety Set, except the percentage for screen failure will be based on all subjects screened and reasons for discontinuation will be based on subjects who discontinued. Phase 1b data and combined Phase 1b and Phase 2 data will be presented separately.

A listing of the subject disposition will be provided. The reason for exclusion from any analysis set will be listed in a separate listing.

10. PROTOCOL DEVIATIONS

A listing will be provided for subjects with protocol deviations during the study. All protocol deviations will be assessed as minor, major, critical or important. The protocol deviation criteria will be described in the protocol deviation management plan. The protocol deviations will be classified as "Major" or "Minor" and Major will be summarized in tables and all deviations will be presented in the listings.

10.1. DEVIATIONS RELATED TO PK OR PHD ANALYSIS

Changes to the procedures or events which may impact the quality of the PK or PHD data, will be considered important protocol deviations or events and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK or PHD. Examples include, but may not be limited to, vomiting following oral dosing occurring within the time frame of 2 times the median time of maximum concentration (t_{max}), sample processing errors that lead to inaccurate bioanalytical results, and/or missed or inaccurate dosing on the day of PK or PHD measurements. In the case of an important protocol deviation or event, affected PK or PHD data will be excluded from any summaries or analyses. Other protocol deviations or events which are not expected to markedly impact the PK or PHD results and associated data interpretation will not be considered important protocol deviations for PK and/or PHD analyses.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAF as all subjects for Phase 1b, and by individual tumor types (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC) for Phase 2, separately. The Phase 2 summaries will be repeated for the FAS set and the PP set respectively if the populations are different.

The following demographic and other baseline characteristics will be reported for this study as frequency (%) for categorical variables and mean (Std, min, max, median) for the continuous variables. Listings of the demographic and other baseline characteristics will also be provided.

The following will be summarized for Phase 1b subjects regardless of tumor types, and combined Phase 1b and Phase 2 subjects in tumor type-specific groups:

- Age (years) – calculated relative to date of consent
- Age Category (<65 years, >=65 to <75, >=75 years)
- Gender (Female and Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not reported)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported/Unknown)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Eastern Cooperative Oncology Group (ECOG) Performance Status (0, 1)

Additional tumor-type specific variables for combined Phase 1b and Phase 2 subjects:

The following will be summarized for Melanoma subjects only (split by Melanoma IO-naïve and treated):

- PD-L1 Level (Positive, Negative, not available)
- BRAF Mutation (Positive [V600E, V600K, Other/Unknown], Negative, Unknown Mutation Status)
- Time since Diagnosis (year)
- Metastatic Stage (M1a/M1b/M1, M1c, M1d, Other at study entry as reported on the eCRF)
- LDH (>ULN, <=ULN)
- Number of Metastatic Sites (>=3, <3; counted as the number of unique organs reported on the Target and Non-target Lesion assessment pages in the eCRF with the assessment code being "Present" or "Unequivocal Progression")
- Tumor Burden (<30mm, >= 30mm)
- Brain Metastases (Yes, No)
- Prior systemic Treatment (0, First line, Second line and up as reported on the Previous Cancer Therapy page of the eCRF)
- Prior Cancer Treatment modality (Chemotherapy, Immunotherapy, Biologic, Combination, Other)

The following will be summarized for NSCLC subjects only (split by NSCLC IO-naïve/treated):

- Smoking Status (Yes [current/former], No)
- Histological Subtype (Squamous Cell NSCLC, Non-squamous Cell NSCLC)
- Metastatic Status (M0, M1)
- Prior Treatment Lines (0, 1, 2 and up as reported on the Previous Cancer Therapy page of the eCRF)
- Prior Cancer Treatment modality (Chemotherapy, Immunotherapy, Biologic, Combination, Other)

The following will be summarized for Renal cell carcinoma subjects only:

- Histological Subtype (Clear Cell RCC, Papillary RCC, Chromophobe RCC, Unclassified RCC, Other)
- Metastatic Status (M0, M1)
- Prior Treatment Lines (0, 1, 2 and up as reported on the Previous Cancer Therapy page of the eCRF)
- Prior cancer Treatment modality (Chemotherapy, Immunotherapy, Biologic, Combination, Other)

Tobacco use will be listed and summarized in a table for combined Phase 1b and Phase 2 NSCLC subjects.

11.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height (m^2)
- Age (year) = (date of informed consent– date of birth +1)/365.25

12. PREVIOUS CANCER THERAPY AND RADIOTHERAPY

Data captured on the "Previous Cancer therapy" and "Previous Radiotherapy" forms of the eCRF will be summarized in the SAF with descriptive statistics. For Phase 1b, this analysis will include all subjects regardless of tumor types. For Phase 2, the Phase 1b and Phase 2 data will be combined and analyzed by tumor type-specific groups (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC). The Phase 2 summaries will be repeated for the FAS set and the PP set respectively if the populations are different.

For previous cancer therapy, the following will be summarized in a table:

- Number of subjects with at least one therapy type
- The type of previous therapy (Chemotherapy, Immunotherapy, Biologic, Combination, Other)
- Purpose (Neoadjuvant, Adjuvant, First line for advanced/metastatic, Second line and up, Other)
- Previous therapy best response
- Reason for Discontinuation

For previous radiotherapy, the following will be summarized:

- Number of subjects with at least one Radiotherapy
- Previous radiotherapy type (Curative, Palliative, Other)
- Previous therapy best response

A listing of the previous cancer therapy and radiotherapy will also be provided.

13. MEDICAL, SURGICAL AND DISEASE HISTORY

The following summaries will be presented for Medical, Surgical, and Disease History information using the SAF will be presented by System Organ Class (SOC) and Preferred Term (PT). For Phase 1b, this analysis will include all subjects regardless of tumor types. For Phase 2, the Phase 1b and Phase 2 data will be combined and analyzed by tumor type-specific groups (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC).

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher.

  Medical History conditions are defined as those conditions which stop prior to or at Screening. Medical history related to study disease are identified by site on eCRF and will be summarized in a separate table.

- Surgical History will be coded using MedDRA version 18.1 or higher.

- Disease History/ Stage of Disease

Listings of the medical, surgical and disease histories will also be provided.

14. PRIOR AND CONCOMITANT MEDICATIONS & PROCEDURES

Summaries for Prior and Concomitant Medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) Anatomical Therapeutic Chemical (ATC) version 01SEP2017E or later and presented for the SAF using Level 3 and preferred term. Concomitant procedures will be coded using MedDRA central coding dictionary, version 18.1 or higher. For Phase 1b, this analysis will include all subjects regardless of tumor types. For Phase 2, the Phase 1b and Phase 2 data will be combined and analyzed by tumor type-specific groups (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC). In addition, listings will be provided for prior and concomitant medications and procedures.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the date of administration of the first dose of HBI-8000.

- 'Concomitant' medications and procedures are those which started prior to, on or after the first dose of HBI-8000 until no later than 30 days following the last dose of HBI-8000 AND ended on or after the date of first dose of study medication or were ongoing within 30 days after the last dose of HBI-8000.

15. STUDY MEDICATION EXPOSURE

Exposure to study medication will be presented for the SAF. For Phase 1b, this analysis will include all subjects regardless of tumor types. For Phase 2, the Phase 1b and Phase 2 data will be combined and analyzed by tumor type-specific groups (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC).

The date of first study medication administration will be taken from the eCRF "HBI-8000 Dosing Administration (HBI)" and "Nivolumab Dosing Administration (NIVO)" forms. The date of last study medication will be taken from the eCRF "End of Study (EOS)" form.

The following data will be summarized in a table:

- Duration of exposure (months) (HBI-8000, and Nivolumab)
  Interruptions, reductions/dose changes, delays, and compliance are not taken into account for duration of exposure (HBI-8000).
- Number of times study drug is administered (HBI-8000)
- Number of cycles administered (HBI-8000, and Nivolumab)
- Cumulative exposure (mg) (HBI-8000).
- Number of cycles with dose interruptions (HBI-8000, Nivolumab, and both HBI-8000 and Nivolumab interrupted)
- Time to 1st dose interruption (days) (HBI-8000, and Nivolumab).
- Time to 1st dose reduction (days) (HBI-8000)
- Action taken and reasons by cycle (HBI-8000).

A listing of the medication exposure for HBI-8000 and Nivolumab will also be provided.

15.1. DERIVATIONS

- Duration of exposure of HBI-8000 (month) = (End date of last study administration – Start date of first study administration + 3) / 30.4375, if date of last study drug minus date of first study drug is multiple of 7. Otherwise, duration of exposure of HBI-8000 (month) = (End date of last study administration – Start date of first study administration + 4) / 30.4375.
- For Phase 1b, Duration of exposure of Nivolumab (month) = (End date of last study administration – Start date of first study administration + 14) / 30.4375.
- For Phase 2, Duration of exposure of Nivolumab (month) = (End date of last study administration – Start date of first study administration + 14) / 30.4375, if the last planned Nivolumab dose was 240 mg. Otherwise, if the last planned Nivolumab dose was 480 mg, duration of exposure of Nivolumab (month) = (End date of last study administration – Start date of first study administration + 28) / 30.4375.

- Number of HBI-8000 cycles administered = Duration of exposure of HBI-8000 (days) / 28.
- Number of Nivolumab cycles administered = Duration of exposure of Nivolumab (days) / 28.
- Cumulative exposure (mg) = Sum of all study drug (HBI-8000) administered (mg)
- Number of cycles with dose interruptions = Sum of the number of cycles when at least one dose interruption occurred, separately for HBI-8000, Nivolumab, and both HBI-8000 and nivolumab interrupted.
- For Phase 1b, Time to 1st dose interruption (days) = Date of the last dose administered prior to dose interruption + x – Date of first dose +1, where x is 3 for HBI-8000, and 14 for Nivolumab.
- For Phase 2, Time to 1st dose interruption (days) = Date of the last dose administered prior to dose interruption + x – Date of first dose +1, where x is 3 for HBI-8000, and 14 for Nivolumab if the last planned dose before the first dose interruption is 240 mg, and 28 for Nivolumab if the last planned dose before the first dose interruption is 480 mg.
- Time to 1st dose reduction (days) (for HBI-8000 only) = Date of the last dose administered prior to dose reduction – Date of first dose +1

16. STUDY MEDICATION COMPLIANCE

Compliance to study medication HBI-8000 will be evaluated by the site at each treatment cycle. Subjects who were at least 75% compliant with study medication during the treatment cycle and subjects who were compliant with dosing regimen based on drug intake diary will be reported on the HBI-8000 Treatment Compliance page of the eCRF. The data will be presented for the SAF set in a table and a listing. Subjects who discontinued from treatment due to "subject non-compliance" will be summarized in the disposition table.

17. OUTCOMES

17.1. PRIMARY OBJECTIVE

The primary objective is to determine Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D) of HBI-8000 and to evaluate frequency and severity of toxicities of this combination treatment based on the frequency of DLTs which occurred within 28 days of the first study drug administration (Cycle 1).

17.1.1. PRIMARY VARIABLE & DERIVATION

The MTD is defined as the dose at which DLT is observed in no more than 1 out of 6 subjects during the first treatment cycle (Cycle 1) and is determined following the conventional 3 +3 design dose escalation schema in Phase 1b.

A DLT is defined as the treatment-related adverse events, graded according to National Cancer

Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, observed during the first 28 days with severity defined in the protocol section 3.2.

17.1.2. Primary Analysis of Primary Variable

The summary of the DLT during the DLT assessment period (Phase 1b) will be provided by SOC and PT.

The incidence of each DLT in Phase 1b will also be tabulated and will be classified by SOC and PT according to severity and relationship to study drug for subjects in the Safety Set.

17.2. Secondary Objective

- To explore the efficacy of study treatment as measured by ORR, DCR, CBR, DoR, and PFS in all subjects treated at RP2D
- To obtain PK of twice weekly HBI-8000 when administered in combination with Nivolumab administered once every two weeks (Phase 1b all sites)
- To obtain PK of twice weekly HBI-8000 when administered in combination with nivolumab administered per package insert dose (Appendix 9 in the Protocol) and administration (Phase 2 selected sites)
- To characterize the effect of HBI-8000 on the electrocardiogram (ECG) QT interval corrected for heart rate (QTc interval) (Phase 1b only)

17.2.1. Efficacy Outcome Variables & Derivations

The following efficacy analyses will be performed for Phase 2 on the Full Analysis Set using the target and non-target lesion assessments which follow the guidelines specified in RECIST criteria 1.1. The Phase 2 analysis will be done by tumor type (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC) using combined data from Phase 1b and Phase 2. The efficacy analysis by tumor type will be performed for Phase 2 if only Phase 2 enrolled subjects of the specified tumor type, or the combined Phase 1b and Phase 2 if subjects of the specified tumor type were enrolled in both Phase 1b and Phase 2. In the latter case, subjects at all dose levels will be combined. The analyses will be repeated for the per protocol set.

- ORR is defined as the percent of subjects with complete response (CR) or partial response (PR) according to RECIST 1.1 criteria. Subjects who do not have an on-study assessment due to safety issues will be included as non-responders.
- DCR is defined as the percent of subjects with CR or PR or stable disease (SD) according to REICIST 1.1 criteria.
- CBR, defined as the percent of subjects with a CR or PR or SD lasting for at least 12 weeks according to RECIST 1.1 criteria.

- DoR applies to subjects with either CR or PR and it is defined as time from the first assessment of CR or PR until the date of the first occurrence of PD, or until the date of death. In the case of a censored event, the duration of response is censored based on the rules specified below.

- PFS, defined as the time from the date of first dose of HBI-8000 until tumor progression by site reported RECIST 1.1, or clinical progression, or death, whichever occurs first. If tumor progression data include more than 1 date of progression, the earliest date will be used. The length of PFS will be calculated as: PFS (months) = [(earliest date of progression/death date [censor date] – first HBI-8000 dosing date) + 1]/30.4375. The clinical progression date is derived using the earliest progression date from target lesion, non-target lesion, investigator overall assessment, new target lesion date from RECIST assessment and the clinical progression date resulting in treatment discontinuation.

If neither progression nor death occur, subjects will be censored as follows:

A. Subjects who have not started new (non-protocol) anti-cancer treatment and have a baseline and at least one on-study disease assessment, will be censored at the date of the last objective disease assessment that verified lack of disease progression.
B. Subjects who have started new (non-protocol) anti-cancer, have a baseline and at least one on-study disease assessment, will be censored at the date of the last objective disease assessment documenting no progression prior to the start of the new treatment. For subjects who discontinued from study treatment due to receiving new anti-cancer treatment, the discontinuation date will be considered as the start of the new treatment. For subjects who received anti-cancer treatment (systemic treatment and non-palliative radiation) during survival follow up, the treatment start date will be reported on the Survival Follow Up page.
C. Subjects who were treated with HBI-8000 and had inadequate post-baseline assessment (e.g. no post-baseline record, or the record indicates "Not Accessed") will be censored at the date of first dose of HBI-8000.

The following subjects will be censored although they have progressed disease or die during the study:

D. Subjects who progressed/died after starting a new anti-cancer treatment will be censored at the date of the last objective disease assessment documenting no progression prior to the start of the new treatment.

The PFS censored rules will be the same as above, but subjects who had anti-cancer treatment will not be censored. Instead, the anti-cancer treatment will be treated as an event, that is PFS (months) = [(progression/death date/date of first anti-cancer treatment – first HBI-8000 dosing date) + 1] / 30.4375.

The frequency of BOR will be summarized by number and percentage of subjects meeting the following: Complete Response, Partial Response, Stable Disease, Progressive Disease, Not Assessed and Not Evaluable. Separate analyses for BOR will be prepared for Target Lesion Assessment (Only) and Investigator Overall Assessment.

Response rate endpoints (ORR, DCR and CBR) will be summarized by number and percentage of subjects meeting the definition of ORR and CBR along with the corresponding exact 95% confidence intervals based on binomial distribution.

Time-to event endpoints (DoR, PFS) will be summarized by Kaplan-Meier methods (median, 95% confidence interval [CI], number of events, and number censored).

Listings of the investigator response assessment, target lesion assessment, non-target lesion assessment and new lesion assessment will be provided.

17.2.2. Pharmacokinetic Outcome Variables & Derivations

Blood samples for measurement of plasma HBI-8000 concentrations will be collected at the times specified in Appendix 2 or in Appendix 3 of the protocol for Phase Ib (Part 1) and Phase II (Part 2), respectively.

A listing of PK blood sample collection times, derived sampling times, and plasma HBI-8000 concentrations from this study will be provided. Data excluded from the PKS due to important protocol deviations or events that affect PK will be flagged. Concentrations in the PKS will be summarized by study part, dose level/treatment, and cycle/study day/measurement time using descriptive statistics (number of subjects [N], number of observations [n], mean, standard deviation, coefficient of variation [CV%], median, minimum, and maximum). A summary of Parts 1 and 2 combined for the RP2D dose will also be included. If n for a summary level is ≥3, all descriptive statistics will be presented; if n = 2, minimum, and maximum will be presented and all other descriptive statistics will be reported as not determined (ND); if n = 1, the single available value will be presented for minimum, and maximum, and all other descriptive statistics will be reported as ND. Concentrations that are BLQ will be treated as zero for the computation of descriptive statistics. Figures of mean ± standard deviation plasma concentration-time profiles on linear and semi-logarithmic scale will be provided by dose group and cycle/study day (for Part 1), and by study part and study day (for RP2D dose level only).

For plasma PK analysis of HBI-8000, predose samples in concentration-time profiles on Cycle 1 Day 1 (C1D1) and Cycle 2 Day 1 (C2D1) that are BLQ or missing will be assigned a numerical value of zero for the calculation of PK parameters. Any quantifiable concentration values observed at predose on C1D1, regardless of magnitude, will be identified in the study report and used for the computation of PK parameters.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to maximum concentration (C_{max}), will be evaluated to determine if an assigned value of zero or missing makes sense. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. Any BLQ values that occur at the end of the collection interval (after the last quantifiable concentration) will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.4 or higher (Certara, L.P., Princeton, New Jersey, United States). Nominal times will be used in calculation of PK parameters for preliminary analyses, and actual elapsed times will be used for calculation of PK parameters for the final analysis.

If data permit, the following plasma PK parameters will be calculated on C1D1 and/or C2D1 for subjects who have serial PK blood samples collected on these days, unless otherwise noted:

$AUC_{(0-7)}$	Area under the plasma concentration-time curve from zero (predose) to 7 hours postdose, calculated by linear up/log down trapezoidal summation. Actual elapsed time at the scheduled 7-hour time point and the associated concentration will be used for calculation of this parameter for the final analysis, except in the following circumstances: If the 7-hour sample is collected outside the protocol-allowed time window relative to the HBI-8000 dose (applies to C1D1 and C2D1), the concentration at the 7-hour time point may be interpolated. If interpolation in such a case is not possible or reasonable, this parameter (and related parameters) will be

	calculated and listed using the actual time/concentration at 7 hours but excluded from descriptive statistics. If the 7-hour sample (applies to C1D1 and C2D1) is missing, this parameter (and related parameters) will not be reported.
$AUC_{(0-7)}/D$	Dose-normalized $AUC_{(0-7)}$, calculated as $AUC_{(0-7)}$ divided by HBI-8000 dose.
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from zero (predose) to 24 hours postdose, calculated by linear up/log down trapezoidal summation. Calculated for C1D1 only. Actual time at the scheduled 24-hour time point and the associated concentration will be used for calculation of this parameter for the final analysis, except in the following circumstances: If the 24-hour sample is collected outside the protocol-allowed time window relative to the HBI-8000 dose, the concentration at the 24-hour time point may be interpolated. If interpolation in such a case is not possible or reasonable, this parameter (and related parameters) will be calculated and listed using the actual time/concentration at 24 hours but excluded from descriptive statistics. If the 24-hour sample is missing, this parameter (and related parameters) will not be reported.
$AUC_{(0-24)}/D$	Dose-normalized $AUC_{(0-24)}$, calculated as $AUC_{(0-24)}$ divided by HBI-8000 dose. Calculated for C1D1 only.
C_{max}	Maximum observed plasma concentration, obtained directly from the observed concentration versus time data.
C_{max}/D	Dose-normalized C_{max}, calculated as C_{max} divided by HBI-8000 dose.
t_{max}	Time of C_{max}, obtained directly from the observed concentration versus time data.
C_{pre}	Predose plasma concentration, obtained directly from the observed concentration versus time data. Calculated for C2D1 only.
C_{pre}/D	Dose-normalized C_{pre}, calculated as C_{pre} divided by HBI-8000 dose. Calculated for C2D1 only.
$AUC_{(0-7)}$ Ratio	Ratio for $AUC_{(0-7)}$ on C2D1 : C1D1, calculated as ($AUC_{(0-7),C2D1}$ / $AUC_{(0-7),C1D1}$).
C_{max} Ratio	Ratio for C_{max} on C2D1 : C1D1, calculated as ($C_{max,C2D1}$ / $C_{max,C1D1}$).

For PK parameters that require dose for calculation, the nominal administered dose will be used, as no dose correction is required (the drug is administered as the free base; see Investigator's Brochure).

Pharmacokinetic parameters for subjects in the PKS will be summarized by study part, dose level/treatment, and cycle/study day using descriptive statistics (N, n, mean, standard deviation, CV%, median, minimum, maximum, geometric mean, and geometric CV%). Geometric mean and geometric CV% will not be provided for t_{max}. A summary of Parts 1 and 2 combined for the RP2D dose will also be included. If n for a summary level is ≥3, all descriptive statistics will be presented; if n = 2, minimum, and maximum will be presented and all other descriptive statistics will be reported as not

determined (ND); if n = 1, the single available value will be presented for minimum, and maximum, and all other descriptive statistics will be reported as ND. Scatter plots of individual and geometric mean values of selected parameters (area under the curve [AUC], C_{max}, C_{pre} [if sufficient values are quantifiable], and corresponding dose normalized parameters) versus dose may be provided if sufficient data are available for these plots (at least 3 dose levels).

Additionally, PK concentration-time data collected in this study will be combined with PK concentration-time data collected from other studies and a population PK analysis will be performed. A separate population PK analysis plan will be written to address the planned population PK analysis. Results of the population PK analysis will be presented in a report separate from the Clinical Study Report (CSR).

17.2.3. QTc Interval Analysis (Holter 12-Lead ECGs)

Holter monitors will be used to record 12-lead continuous digital ECGs at all the clinical sites on the study days specified in Appendix 1 of the protocol (Phase 1b only). Triplicate 10-second ECGs will be extracted from the Holter flashcard at each of the specified time points and analyzed for PR, QRS, RR, and QT intervals by the Central ECG Laboratory at the time points specified in Appendix 2 of the protocol.

The measured QT data will be corrected for heart rate using Fridericia (QTcF).

The heart-rate corrected QT intervals will be calculated using the following formulae, if these are not supplied in the source data:

- Fridericia Correction: $QTcF=QT/ RR^{0.33}$

All derivations and analyses of ECG intervals will be based on the mean of the replicate ECG intervals at each assessment.

Observed and change-from-baseline QT and QTc and other ECG intervals will be listed. Baseline for postdose Holter ECG measurements are the time-matched measurement on the Baseline day. Data excluded from the PDS due to important protocol deviations or events that affect PHD will be flagged. Data in the PDS will be summarized by study part, dose level/treatment, and cycle/study day/measurement time using descriptive statistics (N, n, mean, standard deviation, CV%, median, minimum, and maximum).

Central lab interpretation of any ECG abnormalities will be listed.

The incidence of clinically noteworthy QTc intervals will be tabulated according to the following criteria. The denominator used will be the number of subjects with ECGs available for the given assessment.

Observed QTc values:

- >500 ms
- >480 ms and ≤500 ms
- >450 ms and ≤480 ms

Change from Baseline values:

- >60 ms
- >30 ms and ≤60 ms

Additionally, QTc data collected from this study will be combined with QTc data collected from other studies, and a statistical assessment of the relationship between QTc and PK concentrations will be performed. A separate analysis plan will be written to address this analysis, and the results will be provided in a separate report.

17.2.4. Concentrations vs QTc Interval Analysis (Holter 12-Lead ECGs)

The effect of HBI-8000 concentrations on the QTcF interval will be assessed by exposure-response (CQT) modelling for Phase 1b only (Garnett & al., 2017).

17.2.5. Model Specification

The assessment of the concentration-QTcF relationship will utilize a random coefficients mixed effects model for the change-from-baseline (ΔQTcF) values with continuous effects for HBI-8000 plasma concentration and baseline value (corrected for overall baseline mean), plus subject-level random effects for intercept and concentration slope under unstructured covariance. Restricted maximum likelihood will be used for estimation. The degrees of freedom estimates will be determined by the Kenward-Roger method. All evaluable concentration-ΔQTcF pairs from the pharmacodynamic set will be included in this model. Concentrations will be analysed on the original scale and BLQ values will be treated as zero.

If the above model fails to converge the following alternatives may be attempted:

- Removing covariance between subject-level random intercept and slope
- Removing subject-level random slope effect
- Standardizing ΔQTcF and/or concentrations values to mean of 0 and SD of 1

From the model the following will be presented:

- the concentration slope and intercept with 95% CI
- the mean ΔQTcF at the geometric mean C_{max} for each dose level with 90% CI.
- A scatterplot of ΔQTcF versus concentration will be produced with the regression line, point estimates of mean ΔQTcF specified above, and 90% confidence bands/intervals overlain
- Mean ΔQTcF and mean HBI-8000 concentration overlaid vs time postdose.

17.2.6. Investigation of Hysteresis

Hysteresis will be assessed based on graphical displays of the mean of ΔQTcF versus time described above. Also for each subject, H = time of maximum ΔQTcF – PK t_{max} will be calculated. If the median value of H is more than 1 hour and is statistically different from zero at $p<0.01$ (one-sided) using a signed-rank test, other exposure-response models including hysteresis effects may be explored.

17.2.7. Assessment of Appropriateness of a Linear Model

Plots of concentration and fitted values vs residuals will be produced with loess lines overlaid. In addition, a model with a quadratic term in concentration will be fitted, and the quadratic term will be tested at the 2-sided 5% level. If there is an indication that a linear model is inappropriate, additional models may be fitted, in particular:

- An E-max model
- A log-transformation model where the HBI-8000 plasma concentration C is replaced by log(C/C0), C0 is the limit of quantification of the assay used to determine C and all values below C0 are replaced by C0 (i.e., log[C0/C0] = 0)

The model parameters and model-predicted ΔQTcF be presented for the model found to best accommodate the nonlinearity detected, if any.

17.2.8. Additional Diagnostics

The following diagnostic plots will be also generated:

- Normal QQ-plots for the residuals, to assess assumption of a normality of residuals
- Residuals vs baseline value, to assess adequacy of the linear covariate
- Residuals vs time, to assess patterns in time effects
- Log QTcF vs Log RR, to assess the adequacy of the QTcF correction for RR
- Mean change-from-baseline RR and mean HBI-8000 concentration overlaid vs time postdose, to assess changes in RR

17.3. Exploratory Objectives

The exploratory objectives are:

- To investigate the kinetics and extent of histone acetylation in PBMC at the RP2D of HBI-8000 (Phase 2 only)
- To explore potential biomarkers for disease response through sequential sampling of blood and /or tumor tissue in subjects consenting to correlative sub-studies at participating sites (Phase 2 only)

Actual and change from baseline biomarkers will be summarized in a table. A listing will be provided.

18. Safety Outcomes

All outputs for safety outcomes will be based on the SAF. Unless otherwise specified in the sections below, safety data from Phase 1b will be summarized by treatment for all subjects regardless of tumor types, and safety data from Phase 2 will be summarized by using combined data from Phase 1b and Phase 2 overall and by tumor type-specific groups (Melanoma IO-naïve/treated, NSCLC IO-naïve/treated, RCC).

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, version 24.0 and NCI CTCAE, Version 4.03 for severity grade.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of HBI-8000.

Adverse events that change in severity grading are reported as new events in eCRF. In the analysis of AEs, a new variable called 'derived AE number' is created to identify and combine all relevant individual AEs in to one record by taking the worst grade, serious event, relationship and action into consideration. Multiple AEs with the same SOC and PT will be collapsed into one AE when an AE with the same SOC and PT starting within one day after the end date of the previous AE.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

18.1.1. ALL AES AND TEAES

All AEs observed during the study will be summarized by SOC and PT. An overview and Incidence of TEAEs will be presented by SOC and PT and also broken down further by maximum severity and relationship to HBI-8000, nivolumab, or both HBI-8000 and Nivolumab (study medication).

- Severity is classed as Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: life-threatening, and Grade 5: death (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

- Relationship to study medication as indicated by the Investigator, is classed as unrelated, unlikely, possible, probable, definite (increasing severity of relationship). A "related" TEAE is defined as a being possibly, probably, or definitely related to the study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

In addition, the following summaries will be performed:

- Incidence of TEAE by severity, related and un-related to study medication (HBI-8000)

- Incidence of TEAEs related to HBI-8000 alone, Nivolumab alone, and both HBI-8000 and Nivolumab

- Incidence of TEAEs with grade >=3 by relationship to HBI-8000 alone, Nivolumab alone, and both HBI-8000 and Nivolumab

- Incidence of TEAEs leading to HBI-8000 dose modification (reduction or interruption) by severity and relationship to study HBI-8000 or Nivolumab

- Incidence of TEAEs leading to Nivolumab dose modification (reduction or interruption) by severity and relationship to study HBI-8000 or Nivolumab

- Incidence of TEAEs leading to discontinuation or withdrawal of HBI-8000 by severity and relationship to HBI-8000 or Nivolumab
- Incidence of TEAEs leading to discontinuation or withdrawal of Nivolumab by severity and relationship to HBI-8000 or Nivolumab

18.1.2. TEAEs Leading to Dose Modification (Dose Reduction or Interruption) of Study Medication

TEAEs leading to Dose Modification (Reduction or Interruption) are those recorded under "Action Taken" on the "HBI-8000 Dosing Administration" and "Nivolumab Dosing Administration" eCRF forms.

The TEAE leading to dose modification of either HBI-8000 or Nivolumab will be summarized by SOC, PT and relationship to HBI-8000 alone, Nivolumab alone, and both HBI-8000 and Nivolumab.

18.1.3. TEAEs Leading to Discontinuation or Withdrawal of Study Medication

TEAEs leading to permanent discontinuation from study will be identified on the "Adverse Event (AE)" forms of the eCRF with "Yes" marked for the question "Did the AE cause the subject to discontinue from the study?". TEAEs leading to withdrawal of HBI-8000 and Nivolumab will be identified as "Drug Withdrawal" on the eCRF under "Actions taken with HBI-8000" and "Actions taken with Nivolumab", respectively.

The incidence of TEAEs leading to discontinuation or withdrawal of HBI-8000 and Nivolumab will be summarized separately by SOC, PT and relationship to HBI-8000 alone, Nivolumab alone, and both HBI-8000 and Nivolumab.

18.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the "Adverse Events" form of the eCRF. The incidence of serious TEAEs by SOC and PT will be prepared. They will also be summarized by relationship to HBI-8000 alone, Nivolumab alone, and both HBI-8000 and Nivolumab.

18.1.5. Adverse Events Leading to Death

AEs leading to Death are those events which are recorded as "Fatal" on the "Adverse Events" form of the eCRF. The incidence of AEs leading to death by SOC and PT will be prepared.

18.1.6. Adverse Events Of Special Interest (AESI)

Data listings will also be provided for the subsections above including TEAEs and Non-TEAEs.

The definition of AE of special interest and Grouped Terms are described in terms of PTs and standardized MedDRA queries (SMQs) in Appendix 3. Note these AESI are characterized as Important risks for the investigational product.

Summaries of incidence rates of TEAEs of special interest will be performed per Grouped Term and

PT.

In the event when the following AEs (AE no. 1 and AE no. 2) occurred within the same subjects, new AESI of the combined AEs will be created, and the most severe grade of the two AEs will be considered as the AE grades for the new AESI. For example, if a subject had both a G3 neutrophil count decreased and a G4 neutropenia. In the AESI table, this subject will be counted once in neutrophil count decreased G3 and once again in neutropenia G4, and once again in the new AESI of 'Neutropenia + neutrophil count decreased' in the G4 category.

Adverse Event No. 1	Adverse Event No. 2	Adverse Event of Special Interest
Leukopenia	White blood cell count decreased	Leukopenia + White blood cell count decreased
Neutropenia	Neutrophil count decreased	Neutropenia + Neutrophil count decreased
Thrombocytopenia	Platelet count decreased	Thrombocytopenia + Platelet count decreased
Anaemia	Haemoglobin decreased	Anaemia + Haemoglobin decreased
Lymphopenia	Lymphocyte count decreased	Lymphopenia + Lymphocytes count decreased

18.1.7. Adverse Events Of Special Interest by Tumor types

Adverse events of special interest will be presented by Melanoma, NSCLC, and RCC.

18.2. Deaths

If any subjects die during the study, a data listing will be provided.

18.3. Laboratory Evaluations

Results will be included in the reporting of this study for hematology, coagulation, urinalysis and serum chemistry including the following parameters:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.
- Coagulation: prothrombin time (PTI), activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR).
- Serum chemistry: blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin (including direct fraction if total bilirubin is elevated), lipase, amylase, thyroid stimulating hormone (TSH), triiodothyroxine (T3), thyroxine (T4) (direct), total protein, albumin, uric acid, alkaline phosphatase, sodium, potassium, calcium, magnesium, phosphorus and glucose.

- Hepatitis B and C panel: HBsAg, anti-HCV antibodies, HCV RNA.
- Urinalysis will be performed by dipstick method followed by microscopic examination in the event of abnormal dipstick results.
- Serum Pregnancy test

Presentations will use SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantitation (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for the hematology, coagulation and serum chemistry laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Summary of laboratory results by CTCAE grades (hematology and serum chemistry only)
- The shift table for CTCAE gradable laboratory parameters will be presented for baseline CTCAE grade versus the worst post-baseline CTCAE grade. The worst grade per subject is defined as the highest CTCAE grade during on-treatment period.
- Listing of subjects meeting abnormal criteria

18.3.1. CTCAE Grading for Laboratory Data

Laboratory measurements will be graded using the CTCAE version 4.03 as defined in the following http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

18.4. Safety ECG Evaluations

Results from QECG using CTCAE version 4.03 will be included in the reporting of this study. All analyses of ECG intervals will be based on the mean of the replicate ECGs at each assessment.

The following ECG parameters will be reported for this study for each time point:

- PR Interval (msec)
- QRS duration (msec)
- QT Interval (msec)
- QTcB Interval (msec)
- QTcF interval (msec)

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- The frequency (%) of subjects with QTcB or QTcF markedly abnormal values (at any post-baseline timepoint)
- Listing of abnormal ECG values

18.4.1. ECG Markedly Abnormal Criteria

Actual values for PR interval, QRS duration, QT interval, QTc interval, and QTcF interval will be provided. Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Increase from baseline QTcB interval > 30 msec, > 60 msec
- Increase from baseline QTcF interval > 30 msec, > 60 msec
- Observed QTcB interval > 450 msec, >480 msec, >500 msec
- Observed QTcF interval > 450 msec, >480 msec, >500 msec

18.5. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Supine Systolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Supine Heart rate (bpm)

The following summaries will be provided for vital signs data:

- Actual and change from baseline
- Listing of subjects meeting abnormal criteria

The following criteria will be used to identify abnormal vital signs:

- Supine Systolic Blood Pressure (mmHg):
  <= 90 mmHg AND change from baseline <= -20 mmHg;
  >= 180 mmHg AND change from baseline >= 20 mmHg
- Supine Diastolic Blood Pressure (mmHg):
  <= 50 mmHg AND change from baseline <= -15 mmHg;
  >= 105 mmHg AND change from baseline >= 15 mmHg

- Supine Heart rate (bpm):
  <= 50 bpm AND change from baseline <= -15 bpm;
  >= 120 bpm AND change from baseline >= 15 bpm

- Weight:
  >= 7% weight loss from baseline;
  >= 7% weight gained from baseline

18.6. PHYSICAL EXAMINATION

The listing for physical examination data by each system (head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems) and separately a listing of abnormal physical examination findings will be provided.

19. DATA NOT SUMMARIZED

The other variables and/or domains not summarized or presented are:

- Serum Pregnancy Test
- Pregnancy Notification
- Hepatitis B and C panel: HBsAg, anti-HCV antibodies, HCV RNA.
- Urinalysis will be performed by dipstick method followed by microscopic examination in the event of abnormal dipstick results.
- Blood transfusions

These domains and/or variables will be presented in a data listing and available in the clinical study database, SDTM and/or ADaM datasets.

References

Garnett, C., & al., e. (2017, December 05). Scientific white paper on concentration-QTc modeling. *Journal of Pharmacokinetics and Pharmacodynamics*. Retrieved from https://doi.org/10.1007/s10928-017-9558-5

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, Std, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places/significant digits, then the summary statistics should have the following decimal places/significant digits:
  - Minimum and maximum: N
  - Mean, median and CV%: N + 1
  - Std: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

  77 (100.0%)
  50 (64.9%)
  0 (0.0%)

- Percentages will be reported to one decimal place, except percentages <100.0% but >99.9% will be presented as '>99.9%' (e.g. 99.99% is presented as >99.9%); and percentages < 0.1% will be presented as '<0.1%' (e.g. 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule. E.g.:

  (<0.1%)
  (6.8%)
  (>99.9%)

- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.

- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

(-0.12, -0.10)
(9.54, 12.91)

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g. 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g. 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

- A "0" should be used to indicate a zero frequency.
- order as what they are defined in the table or listing, from left to right.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY and HH:MM.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	Tables and Figures	Listings
HBI-8000-302 20mg	20mg	20mg
HBI-8000-302	30mg	30mg

Treatment Group	Tables and Figures	Listings
30mg		
HBI-8000-302 40mg	40mg	40mg

HBI 8000-302 20mg is the lowest starting dose for protocol HBI 8000-302, however, if more than 2 subjects experienced DLT in Cycle 1 then the dose will be reduced to 50% of the starting dose to 10mg in the next dose cohort . Please refer to section 3.2.1 of the Protocol for details.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day

START DATE	STOP DATE	ACTION
		and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. ADVERSE EVENTS OF SPECIAL INTEREST

AESI group	Term level	Term	Code
Thrombocytopenia	SMQ	Haematopoietic thrombocytopenia (SMQ) (narrow)	20000031
	PT	Thrombocytopenia + Platelet count decreased	
Neutropenia	PT	Agranulocytosis	10001507
	PT	Autoimmune neutropenia	10055128
	PT	Cyclic neutropenia	10053176
	PT	Febrile neutropenia	10016288
	PT	Granulocyte count decreased	10018681
	PT	Granulocytopenia	10018687
	PT	Idiopathic neutropenia	10051645
	PT	Leukopenia	10024384
	PT	Myelocyte count decreased	10050986
	PT	Myelocyte percentage decreased	10052227
	PT	Neutropenia	10029354
	PT	Neutrophil count decreased	10029366
	PT	Neutrophil percentage decreased	10052223
	PT	White blood cell analysis abnormal	10073323
	PT	White blood cell count decreased	10047942
	PT	Neutropenia + Neutrophil count decreased	
	PT	Leukopenia + White blood cell count decreased	
Infection	SOC	Infections and infestations	10021881
Viral reactivation	PT	Acquired immunodeficiency syndrome	10000565
	PT	Acute hepatitis B	10059193
	PT	Acute hepatitis C	10065051
	PT	Acute HIV infection	10000807
	PT	Adenoviral hepatitis	10056885
	PT	AIDS cholangiopathy	10067092
	PT	AIDS related complex	10001513
	PT	AIDS related complication	10061624

AESI group	Term level	Term	Code
	PT	AIDS retinopathy	10053227
	PT	Asymptomatic HIV infection	10003581
	PT	Asymptomatic viral hepatitis	10063838
	PT	BK virus infection	10055181
	PT	Blood HCV RNA below assay limit	10076955
	PT	Blood HIV RNA below assay limit	10049829
	PT	Blood HIV RNA decreased	10049828
	PT	Blood HIV RNA increased	10049827
	PT	Chronic hepatitis B	10008910
	PT	Chronic hepatitis C	10008912
	PT	Congenital hepatitis B infection	10010496
	PT	Cytomegalovirus chorioretinitis	10048843
	PT	Cytomegalovirus colitis	10048983
	PT	Cytomegalovirus duodenitis	10049014
	PT	Cytomegalovirus enteritis	10049074
	PT	Cytomegalovirus enterocolitis	10049015
	PT	Cytomegalovirus gastritis	10049016
	PT	Cytomegalovirus gastroenteritis	10051349
	PT	Cytomegalovirus gastrointestinal infection	10052817
	PT	Cytomegalovirus gastrointestinal ulcer	10075619
	PT	Cytomegalovirus hepatitis	10011830
	PT	Cytomegalovirus infection	10011831
	PT	Cytomegalovirus mononucleosis	10011834
	PT	Cytomegalovirus mucocutaneous ulcer	10065036
	PT	Cytomegalovirus myelomeningoradiculitis	10065621
	PT	Cytomegalovirus myocarditis	10056261
	PT	Cytomegalovirus oesophagitis	10049018
	PT	Cytomegalovirus pancreatitis	10049566
	PT	Cytomegalovirus pericarditis	10056721
	PT	Cytomegalovirus syndrome	10056262

AESI group	Term level	Term	Code
	PT	Cytomegalovirus test positive	10051620
	PT	Cytomegalovirus urinary tract infection	10051350
	PT	Cytomegalovirus viraemia	10058854
	PT	Disseminated cytomegaloviral infection	10049075
	PT	Disseminated varicella zoster vaccine virus infection	10076667
	PT	Encephalitis cytomegalovirus	10014586
	PT	Encephalitis post varicella	10014603
	PT	End stage AIDS	10049076
	PT	Enterocolitis AIDS	10014894
	PT	Epstein-Barr viraemia	10065110
	PT	Epstein-Barr virus antibody	10053817
	PT	Epstein-Barr virus antibody positive	10052324
	PT	Epstein-Barr virus antigen positive	10052363
	PT	Epstein-Barr virus infection	10015108
	PT	Epstein-Barr virus test positive	10064545
	PT	HBV-DNA polymerase increased	10058937
	PT	Hepatic candidiasis	10049653
	PT	Hepatic gas gangrene	10077055
	PT	Hepatitis A	10019719
	PT	Hepatitis A antibody	10019721
	PT	Hepatitis A antibody abnormal	10019722
	PT	Hepatitis A antibody normal	10019724
	PT	Hepatitis A antibody positive	10019725
	PT	Hepatitis A antigen	10073224
	PT	Hepatitis A antigen positive	10058751
	PT	Hepatitis A virus test positive	10070216
	PT	Hepatitis B	10019731
	PT	Hepatitis B antibody	10019732
	PT	Hepatitis B antibody abnormal	10019733
	PT	Hepatitis B antibody normal	10019735

AESI group	Term level	Term	Code
	PT	Hepatitis B antibody positive	10019736
	PT	Hepatitis B antigen	10063414
	PT	Hepatitis B antigen positive	10063411
	PT	Hepatitis B core antibody	10071342
	PT	Hepatitis B core antibody positive	10071344
	PT	Hepatitis B core antigen	10051160
	PT	Hepatitis B core antigen positive	10052328
	PT	Hepatitis B DNA assay positive	10060047
	PT	Hepatitis B DNA decreased	10068380
	PT	Hepatitis B DNA increased	10068379
	PT	Hepatitis B e antibody	10071343
	PT	Hepatitis B e antibody positive	10071348
	PT	Hepatitis B e antigen	10050914
	PT	Hepatitis B e antigen positive	10052329
	PT	Hepatitis B surface antibody	10063051
	PT	Hepatitis B surface antibody positive	10071346
	PT	Hepatitis B surface antigen	10050529
	PT	Hepatitis B surface antigen positive	10019742
	PT	Hepatitis B virus test positive	10070217
	PT	Hepatitis C	10019744
	PT	Hepatitis C antibody	10019745
	PT	Hepatitis C antibody positive	10019747
	PT	Hepatitis C core antibody	10077053
	PT	Hepatitis C core antibody positive	10077052
	PT	Hepatitis C RNA	10019748
	PT	Hepatitis C RNA decreased	10068378
	PT	Hepatitis C RNA fluctuation	10068727
	PT	Hepatitis C RNA increased	10068377
	PT	Hepatitis C RNA positive	10019750
	PT	Hepatitis C virus test positive	10070218

AESI group	Term level	Term	Code
	PT	Hepatitis D	10019762
	PT	Hepatitis D antibody	10059538
	PT	Hepatitis D antibody positive	10059528
	PT	Hepatitis D antigen	10058437
	PT	Hepatitis D antigen positive	10058436
	PT	Hepatitis D RNA	10059541
	PT	Hepatitis D RNA positive	10059540
	PT	Hepatitis D virus test positive	10070626
	PT	Hepatitis E	10019768
	PT	Hepatitis E antibody	10057992
	PT	Hepatitis E antibody abnormal	10057994
	PT	Hepatitis E antibody positive	10057985
	PT	Hepatitis E antigen	10060028
	PT	Hepatitis E antigen positive	10060049
	PT	Hepatitis E virus test positive	10070220
	PT	Hepatitis F	10019771
	PT	Hepatitis G	10019773
	PT	Hepatitis H	10019776
	PT	Hepatitis infectious mononucleosis	10019781
	PT	Hepatitis mumps	10019783
	PT	Hepatitis non-A non-B	10019786
	PT	Hepatitis non-A non-B non-C	10019787
	PT	Hepatitis post transfusion	10019791
	PT	Hepatitis toxoplasmal	10019798
	PT	Hepatitis viral	10019799
	PT	Hepatitis viral test positive	10072748
	PT	Hepatitis virus-associated nephropathy	10068610
	PT	Hepatosplenic candidiasis	10051590
	PT	Herpes simplex encephalitis	10019953
	PT	Herpes simplex hepatitis	10067389

AESI group	Term level	Term	Code
	PT	Herpes zoster	10019974
	PT	Herpes zoster cutaneous disseminated	10074297
	PT	Herpes zoster disseminated	10065038
	PT	Herpes zoster infection neurological	10061208
	PT	Herpes zoster oticus	10063491
	PT	HIV antibody	10058761
	PT	HIV antibody positive	10058736
	PT	HIV antigen	10058763
	PT	HIV antigen positive	10058737
	PT	HIV associated nephropathy	10070737
	PT	HIV cardiomyopathy	10069658
	PT	HIV enteropathy	10069691
	PT	HIV infection	10020161
	PT	HIV infection CDC category A	10075708
	PT	HIV infection CDC category B	10075709
	PT	HIV infection CDC category C	10075710
	PT	HIV infection CDC Group I	10020162
	PT	HIV infection CDC Group II	10020163
	PT	HIV infection CDC Group III	10020164
	PT	HIV infection CDC group IV	10061519
	PT	HIV infection CDC Group IV subgroup A	10020166
	PT	HIV infection CDC Group IV subgroup B	10020167
	PT	HIV infection CDC Group IV subgroup C1	10020168
	PT	HIV infection CDC Group IV subgroup C2	10020169
	PT	HIV infection CDC Group IV subgroup D	10020170
	PT	HIV infection CDC Group IV subgroup E	10020171
	PT	HIV infection WHO clinical stage I	10064446
	PT	HIV infection WHO clinical stage II	10064447
	PT	HIV infection WHO clinical stage III	10064448
	PT	HIV infection WHO clinical stage IV	10064456

AESI group	Term level	Term	Code
	PT	HIV peripheral neuropathy	10065681
	PT	HIV test positive	10020188
	PT	HIV wasting syndrome	10050309
	PT	Human herpes virus 6 serology positive	10060827
	PT	Human herpes virus 8 test positive	10071210
	PT	Human herpesvirus 8 infection	10066435
	PT	Human polyomavirus infection	10057366
	PT	Infectious mononucleosis	10021914
	PT	JC virus CSF test positive	10078957
	PT	JC virus infection	10023163
	PT	Kaposi's sarcoma AIDS related	10023286
	PT	Lymphoproliferative disorder	10061232
	PT	Lymphoproliferative disorder in remission	10061233
	PT	Meningitis herpes	10027242
	PT	Multipathogen PCR test	10077018
	PT	Ophthalmic herpes simplex	10073938
	PT	Ophthalmic herpes zoster	10030865
	PT	Oral hairy leukoplakia	10030979
	PT	Perinatal HIV infection	10071049
	PT	Persistent generalised lymphadenopathy	10049025
	PT	Pneumonia cytomegaloviral	10035676
	PT	Pneumonia herpes viral	10035703
	PT	Polyomavirus test positive	10070342
	PT	Polyomavirus-associated nephropathy	10065381
	PT	Progressive multifocal leukoencephalopathy	10036807
	PT	Retroviral infection	10061493
	PT	Retroviral rebound syndrome	10065989
	PT	Sustained viral response	10076041
	PT	Varicella	10046980
	PT	Varicella virus test positive	10070214

AESI group	Term level	Term	Code
	PT	Viral hepatitis carrier	10047458
	PT	Viral test positive	10059424
Torsade de pointes/QT prolongation	SMQ	Torsade de pointes/QT prolongation (SMQ) (narrow)	20000001
Hypersensitivity	SMQ	Anaphylactic reaction (SMQ) (narrow)	20000021
	SMQ	Severe cutaneous adverse reactions (SMQ) (narrow)	20000020
	PT	Drug hypersensitivity	10013700
	PT	Hypersensitivity	10020751
Interstitial lung disease	SMQ	Interstitial lung disease (SMQ) (narrow)	20000042
Cardiac disorder	SOC	Cardiac disorders	10007541
Hepatic disorder excluding virus reactivation	SMQ	Congenital, familial, neonatal and genetic disorders of the liver (SMQ) (narrow)	20000014
	SMQ	Drug related hepatic disorders - comprehensive search (SMQ) (narrow)	20000006
	SMQ	Hepatic disorders specifically reported as alcohol-related (SMQ) (narrow)	20000017
	SMQ	Pregnancy-related hepatic disorders (SMQ) (narrow)	20000018
	PT	Hepatic echinococciasis	10019659
	PT	Hepatitis syphilitic	10019794
	PT	Liver abscess	10024652
	PT	Portal pyaemia	10036202
	PT	Schistosomiasis liver	10039610
	PT	Weil's disease	10047903
	PT	Hepatic cyst infection	10051705
	PT	Gianotti-Crosti syndrome	10053842
	PT	Hepatic infection	10056522
	PT	Hepatobiliary infection	10056523
	PT	Hepatitis B reactivation	10058827
	PT	Hepatic amoebiasis	10063741

AESI group	Term level	Term	Code
	PT	Hepatic infection bacterial	10065215
	PT	Hepatic infection helminthic	10065216
	PT	Hepatic infection fungal	10065217
	PT	Withdrawal hepatitis	10071220
	PT	Perinatal HBV infection	10075233
	PT	Hepatosplenic abscess	10077631
Anemia	PT	Anemia	10002034
	PT	Hemoglobin decreased	10018884
	PT	Anemia + Hemoglobin decreased	
Lymphopenia	PT	Lymphopenia	10025327
	PT	Lymphocyte count decreased	10025256
	PT	Lymphopenia + Lymphocytes count decreased	
Hypokalemia and Hyponatremia	SMQ	Hypokalaemia (SMQ) (narrow)	20000233
	SMQ	Hyponatraemia/SIADH (SMQ) (narrow)	20000141

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]