CLINICAL STUDY PROTOCOL

Protocol Title:	**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)**
Protocol Number:	**HBI-8000-302**
Date of Protocol:	**05 October 2022**
Product:	**HBI-8000**
IND No.:	[redacted]
Study Phase:	**1b/2**
Sponsor:	**HUYABIO International LLC** **12531 High Bluff Drive, Suite 138** **San Diego, CA 92130** **USA**

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CONFIDENTIAL

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed written consent of HUYABIO International, LLC.

The study will be conducted according to the International Council for Harmonization harmonized tripartite guideline E6 (R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: 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)

Chief Medical Officer
HUYABIO International, LLC
San Diego, CA
United States of America

SUMMARY OF CHANGES SINCE LAST VERSION

Changes from Version 7.0 to Version 8.0		
Section		**Change**
Title Page, header, signature page		Updated version number
Summary of Changes Since Last Version		Added abbreviated summary of changes since last version
Protocol Synopsis		Noted that with Protocol Amendment v8.0, remaining subjects in the Extension Phase of the study will receive the HBI-8000 treatment as film coated tablets.
5.2	Identity of Investigational Product(s) Table 2: Investigational Products	Updated and revised HBI-8000 Investigational Product from uncoated to film coated tablets, including manufacturing details, and manufacturer name and location
5.4	Investigational Products Storage	Updated HBI-8000 storage and distribution condition.

PROTOCOL SYNOPSIS

Study 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)

Name of Sponsor/ Company:	HUYABIO International, LLC
Name of Finished Product:	HBI-8000 (Tucidinostat, chidamide)
Title of Study:	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)
Protocol No:	HBI-8000-302
Lead Investigator:	[redacted] H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
Indication	Advanced solid tumors: Melanoma, RCC, NSCLC
Study center(s):	Multicenter study (United States [US]): Dose Escalation (Phase 1b): 4-6 sites Cohort Expansion (Phase 2): 12-16 sites
Study duration: The study will include a screening period (up to 28 days), up to 24 months of treatment until disease progression or unacceptable toxicity, and up to 12 months post-last treatment of HBI-8000 for tumor response until disease progression, start of new anti-cancer treatment, or referral to hospice for subjects discontinuing without progression. Subjects with clinical benefit at end of the main study may continue HBI-8000 treatment in Extension Phase until disease progression, unacceptable toxicities, initiation of another anti-cancer treatment, referral to hospice, discretion of the investigator or consent withdrawal.	**Phase:** 1b/2
Study Treatment	HBI-8000 tablet: Phase 1b: at 20, 30, 40 mg/dose, orally twice a week until maximum tolerated dose (MTD) Phase 2: at MTD from Phase 1b or 40 mg if MTD is not reached Nivolumab IV: Phase 1b: 240 mg intravenous infusions every 2 weeks. Phase 2: In accordance with the manufacturer prescribing information and dosing information (Appendix 9) and institution's prescribing practice. A treatment cycle consists of 28 days. Treatment continues until disease progression or unacceptable toxicity. Should toxicity be deemed not related to nivolumab, subject may continue to receive nivolumab at the discretion of Investigator

Objectives:

Primary:

- 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

Secondary:

- 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 pharmacokinetics (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 manufacturer dosing information (Appendix 9) (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)

Exploratory:

- 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)

Study design	This is a multicenter, Phase 1b/2 dose finding trial of HBI-8000 in combination with 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 to Protocol Amendment v4.0, 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 v5.0, 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 v6.0, only subjects with advanced cutaneous melanoma who have not been treated with 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 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 experiences DLT, escalation to next higher dose is allowed. The RP2D will be confirmed in at least 6 evaluable subjects. In Phase 2 (Part 2), 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 programmed death-ligand 1 (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 enrollment. Preliminary efficacy will be explored for each indication in subjects enrolled in Phase 1b and Phase 2. With Protocol Amendment v7.0, subjects with clinical benefit at the time of the data cut-off for the main study will be entered in the Extension Phase of the study to continue HBI-8000 treatment and be monitored for safety. With Protocol Amendment v8.0, remaining subjects in the Extension Phase of the study will receive the HBI-8000 treatment as film coated tablets.
Planned number of subjects:	Dose Escalation Phase: Up to 18 subjects Cohort Expansion Phase: Up to 100 subjects: melanoma (up to 60 subjects) and NSCLC (up to 40 subjects) Extension Phase: Up to 2 subjects
Diagnosis and main criteria for inclusion:	Subjects with advanced melanoma, RCC and NSCLC being treated with nivolumab as approved by FDA. **Inclusion Criteria** Subjects may be entered in the study only if they meet **all** of the following criteria: 1. Adults at least 18 years of age. 2. Eastern Cooperative Oncology Group (ECOG) performance status ≤1. 3. a. Subjects with histopathologically or cytologically confirmed diagnosis of non-uveal melanoma, RCC or NSCLC, for whom the use of nivolumab is indicated. NSCLC subjects with EGFR or ALK genomic aberrations in tumor should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab. **(Phase 1b)**. b. Subjects with histopathologically or cytologically confirmed diagnosis of non-uveal melanoma, or NSCLC, for whom the use of nivolumab is indicated **(Phase 2 expansion)**. With Protocol Amendment 5, subjects with NSCLC are not eligible for enrollment. c. Non-uveal melanoma patients whose disease has progressed after achieving stable disease (SD) for at least 3 months, with partial response (PR) or complete response (CR) as the best response that has been documented by imaging studies on previous treatment with a PD-L1 inhibitor with proven efficacy (**Phase 2 expansion)**. With Protocol Amendment 5, subjects with NSCLC are not eligible for enrollment. d. 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). 4. Subject must have at least one measurable target lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Melanoma subjects participating in the optional serial tumor biopsy sub-study must have tumor tissue available from a metastatic or unresectable site for PD-L1 and correlative biomarker analysis. 5. All prior systemic therapy (chemotherapy, mutation targeting therapy, immune checkpoint therapy), surgical or radiation treatment must have been completed at least 4 weeks before study drug administration (2 weeks for palliative radiotherapy, 1 week for minor surgery) pending full recovery from therapy. 6. The following laboratory results within 7 days prior to study drug administration: Adequate hematopoietic, electrolyte, hepatic, and renal laboratory findings as defined below: white blood cells (WBC) ≥3000/μL, neutrophils ≥1500/μL, platelets ≥100x10^3/μL, hemoglobin ≥9.0 g/dL independent of transfusion,

creatinine ≤1.5 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN), alkaline phosphatase ≤2.5 x ULN unless bone metastases present, bilirubin ≤1.5 x ULN (unless known Gilbert's disease where it must be ≤3 x ULN) and serum albumin ≥3.0 g/dL.
7. Life expectancy ≥12 weeks.
8. A negative serum pregnancy test at baseline for women of childbearing potential.
9. Are willing to abstain from heterosexual activity or practice physical barrier contraception prior to time of study entry to at least 5 months after the last day of treatment.
10. Have the ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

Subjects who fulfill **any** of the following criteria at screening will **not** be eligible for admission into the study:

1. History of Grade 3 or above hypersensitivity reactions to other monoclonal antibodies.
2. Subjects with a history of a cardiovascular illness including: congestive heart failure (New York Heart Association Grade III or IV); unstable angina or myocardial infarction within the previous 6 months; or symptomatic cardiac arrhythmia despite medical management. In addition, for Phase 1b only: QTc using Fridericia's correction formula (QTcF) >450 ms in male, and >470 ms in female, congenital long QT syndrome.
3. Uncontrolled hypertension, systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg.
4. Subjects with active brain metastasis; previously treated brain metastasis is allowed if it has been stable for 4 weeks or more and not requiring steroids.
5. Presence of leptomeningeal disease.
6. History of hemorrhagic diarrhea, inflammatory bowel disease, active uncontrolled peptic ulcer disease or recurrent pleural effusion requiring repetitive palliative thoracentesis within 3 months prior to study entry, except for subjects with a pleurex port; and immune-mediated toxicity leading to treatment discontinuation.
7. Active, known, or suspected serious autoimmune disease, except for type I diabetes mellitus, hypothyroidism only requiring hormone replacement, and skin disorders (such as vitiligo, psoriasis, or alopecia).
8. Active uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
9. Known history of testing positive for human immunodeficiency virus (HIV), known acquired immunodeficiency syndrome (AIDS).
10. Active hepatitis B (serum hepatitis B surface antigen [HBV sAg] positive), or hepatitis C (hepatitis C virus [HCV] antibody test or serum hepatitis C ribonucleic acid [RNA] positive) indicating acute or chronic infection.
11. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted.
12. Use of other investigational agent (drug not marketed for any indication) within 28 days or at least 5 half-lives (whichever is shorter) before study drug administration.
13. Pregnant or breast-feeding women.
14. Second malignancy unless in remission for 2 years, except for non-melanomatous skin cancer, carcinoma *in situ* of the cervix treated with curative intent, curatively treated prostate cancer with prostate-specific antigen (PSA) <0.1 ng/mL.

	15. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events. 16. Unwilling or unable to comply with procedures required in this protocol.

Criteria for evaluation:

Safety Endpoints:

Adverse events and DLTs reported by the subjects or observed during physical examination, vital signs assessment, ECGs, and laboratory tests will be recorded by frequency and severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03 and association with study treatment will be assessed. Eastern Cooperative Oncology Group (ECOG) performance status will be monitored.

Definition of DLT:

A DLT is defined as the following treatment-related adverse events, graded according to NCI-CTCAE v 4.03, observed during the first 28 days.

A. Hepatic non-hematologic DLT

Any one of the following events will be considered a hepatic DLT (irrespective of whether it is considered to be an immuno-related adverse event [irAE]):

- Isolated Grade 4 AST/ALT
- Isolated Grade 3 AST/ALT that fails to return to Grade 1 or less within 5 days
- Isolated total bilirubin ≥Grade 3
- AST or ALT >3 x ULN AND concurrent total bilirubin >2 x ULN

B. Non-hepatic non-hematologic DLT

Any Grade 3 or greater non-hepatic non-hematologic toxicity will be considered as a DLT with the following specific **exceptions**:

- Grade 3 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention.
- Grade 3 nausea or vomiting that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention.
- Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis.
- Isolated Grade 3 fever that lasts ≤3 days and is not associated with hemodynamic compromise (i.e., hypotension, clinical or laboratory evidence of impaired end-organ perfusion)

C. Dose-limiting immune-related toxicities

- Any Grade 2 or greater eye pain or reduction in visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy or any Grade 2 or greater eye pain or reduction in visual acuity that requires systemic treatment.
- Any other Grade 3 or greater irAE

D. Infusion reaction and DLT

- Grade 3 or Grade 4 infusion reactions will also be considered as DLTs.

E. Hematologic DLT

- Grade 4 neutropenia ≥7 days in duration
- Grade 4 thrombocytopenia, or any Grade 3 thrombocytopenia associated with clinically-significant bleeding
- Grade ≥3 febrile neutropenia
- Grade ≥3 hemolysis

Efficacy Endpoints:

Target and non-target lesions assessments will be obtained at screening for baseline assessment, in the last week of the second cycle including C3D1, and then every 8 weeks (±3 days) thereafter.

Tumor assessments will follow guidelines specified in RECIST criteria v1.1 and immune-related Response Evaluation Criteria in Solid Tumors (iRECIST).

- Objective Response (CR+PR) Rate (ORR)
- Disease Control (CR+PR+SD) Rate (DCR)
- Clinical Benefit Rate (CBR), CR, PR, and if SD, ≥12 weeks
- Duration of Response (DoR)
- Progression-Free Survival (PFS)

After the discontinuation of HBI-8000 subjects without disease progression will be followed for tumor assessment with imaging of measurable disease every 12 (±1) weeks until progression, initiation of another anti-cancer treatment, or referral to hospice (unless consent is withdrawn), for up to 12 months after the last dose of HBI-8000 or end of the main study.

Pharmacokinetics

A population PK analysis for HBI-8000 will be conducted in Phase 1b and Phase 2 based on a sparse sampling schema.

Pharmacodynamics

- Holter ECG (QTc) (Phase 1b only)

  In Phase 1b, in conjunction with the population PK analysis, a QTc sub-study will obtain Holter 12-lead ECG measurements in triplicate to investigate the effect of HBI-8000, if any, on QTc intervals

- PBMC histone acetylation (Phase 2 only)

Immune modulation

- Peripheral blood for clinical laboratory variables, molecular characterization for RNA transcripts, tumor tissue genomic profiles will be obtained in subjects consenting to correlative sub-studies at participating sites (Phase 2 only)

Statistical methods:

Based on an assumption of 3 dose levels tested, it is anticipated that up to 18 subjects will be enrolled into the Phase 1b (Part 1) of this study. If necessary additional dose levels may be included to evaluate dose level(s) below the starting dose of 20 mg, twice a week.

In Phase 2, RP2D of HBI-8000 will be evaluated by specific tumor indications. To get preliminary efficacy data and confirm safety, up to approximately 20 subjects who have not been treated with PD-L1 inhibitor and 20 subjects previously treated with at least a PD-L1 with NSCLC, and 20 PD-L1-treated subjects with melanoma will be enrolled. For melanoma subjects who are PD-L1 inhibitor-naïve, up to approximately 40 subjects will be enrolled. Within the same indication, subjects enrolled in Phase 1b portion of the study may be analyzed with those in Phase 2 portion.

The final number of subjects for the entire study will depend on the DLT observed within a dose level, the number of dose levels tested before RP2D is established and patient populations evaluated in this study.

Statistical analyses of safety, tolerability, and anti-tumor activity will be primarily descriptive in nature, as the goal of the study is to determine the DLTs, MTD, and/or RP2D of HBI-8000 to be used for further investigation in combination with standard dose and regimen of nivolumab. This goal will be achieved by the results of a deterministic algorithm; thus, statistical hypothesis testing is neither intended nor appropriate within this context.

Toxicities will be tabulated by type and grade. The safety population will consist of all subjects who received at least 1 dose of HBI-8000.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage

(n, %) of subjects within each dose level. Time to event variables (i.e., PFS, DoR) will be analyzed using Kaplan-Meier methods.

All subjects who received any amount of study treatment (Safety Population) will be included in the final summaries and listings of the safety data.

PK and ECG (QTc) data collected in this study will be combined with data collected from other studies and a population PK analysis and concentration-QTc analysis will be performed. Results of these analyses will be provided in separate reports.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
acH3	Acetylated histone H3
acH4	Acetylated histone H4
ACS	American Cancer Society
ADL	Activities of daily living
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
API	Active pharmaceutical ingredient
APL	Acute promyelocytic leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AUC_{0-t}	Area under curve from time 0 to the last measurable concentration
BIW	2 times a week
BRAF	B-Raf proto-oncogene, serine/threonine kinase gene
BUN	Blood urea nitrogen
CBR	Clinical benefit rate
CFDA	China Food and Drug Administration
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Peak plasma drug concentration
CPI	Checkpoint inhibitor
CR	Complete response
cRA	13-*cis*-retinoic acid
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DCR	Disease control rate
DL	Dose level

DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
EoT	End-of-treatment
ESF	Eligibility screening form
FACS	Fluorescence activated cell sorting
FDA	Food and Drug Administration (US)
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
HBV sAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
HDPE	High-density polyethylene
HEENT	Head, eye, ear, nose, and throat
HIF	Hypoxia inducible factor
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HR	Hazard ratio
HSP	Heat shock protein
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
iCPD	Immune confirmed progressive disease
iCR	Immune complete response
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
INR	International normalized ratio
iPR	Immune partial response
irAE	Immuno-related Adverse Event

IRB	Institutional Review Board
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
iSD	Immune stable disease
iUPD	Immune unconfirmed progressive disease
IV	Intravenous
K_2EDTA	Dipotassium EDTA
LC-MS/MS	Liquid chromatography-mass spectroscopy
LDH	Lactate dehydrogenase
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MHC	Major histocompatibility complex
MICA	MHC Class I chain-related protein A
MICB	MHC Class I chain-related protein B
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Protein kinase mTOR, mechanistic target of rapamycin, also known as mammalian target of rapamycin
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NKG2D	Natural-killer group 2, member D
NMR	Nuclear magnetic resonance
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PK	Pharmacokinetics
POPK	Population pharmacokinetic
PR	Partial response
PRAME	Preferentially expressed antigen in melanoma
PSA	Prostate specific antigen
PT	Prothrombin time
PTCL	Peripheral T-cell lymphoma

Q2W	Every 2 weeks
Q3W	Every 3 weeks
QTcF	QT interval corrected by heart rate, using Fridericia's correction formula
RA	Retinoic acid
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAHA	Suberoylanilide hydroxamine
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
siRNA	Small interfering RNA
SOP	Standard operating procedure
SUSAR	Serious and unexpected suspected adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TGF-β	Tumor growth factor β
TIW	3 times a week
TKI	Tyrosine kinase inhibitor
T_{max}	Time to peak plasma drug concentration
T_{min}	Time to minimum observed plasma concentration
TPS	Tumor proportion score
Treg	Regulatory T cell
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
VEGF-R	Vascular endothelial growth factor R
VHL	Von Hippel-Lindau
VPA	Valproic acid
Vz/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	WHO drug dictionary enhanced

1 INTRODUCTION

1.1 Background Information

1.1.1 Diseases under Study and Their Treatments

1.1.1.1 Melanoma

Melanoma is the most serious form of skin cancer, with a high level of mortality related to unresectable and metastatic melanoma; with the 5-year survival rate for late-stage disease being only 17% according to the American Cancer Society (ACS) [ACS, 2016]. It was estimated that in the United States (US) in 2016, 76,380 new cases of melanoma would be diagnosed, and 10,130 deaths from melanoma would occur [ACS, 2016].

Until recently dacarbazine was a commonly used therapy in subjects with previously untreated melanoma without a B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*) mutation and it is associated with a median overall survival (OS) of 5.6 to 7.8 months [Robert et al., 2011a; Espinosa et al., 2015]. Palliative therapy for advanced disease also includes taxanes, interferons, and interleukin (IL)-2 [Dummer et al., 2010].

Ipilimumab is an anti-cytotoxic T lymphocyte associated antigen-4 (CTLA-4) blocking antibody that has been shown to improve survival at 2 years in previously treated subjects with metastatic melanoma and previously untreated subjects who also received dacarbazine [Hodi et al., 2010; Robert et al., 2011a].

Inhibitors of BRAF [Zelboraf®(vemurafenib) USPI, 2020] and mitogen-activated protein kinase (MEK) [trametinib, cobimetinib] have been associated with a median OS advantage of 13 to 20 months over chemotherapy [Chapman et al., 2011; Flaherty et al., 2012; McArthur et al., 2014]. The objective response ORR rate is high with these agents (45% to 53%), but the median duration of response (DoR) is less than 1 year [Chapman et al., 2011; Flaherty et al., 2012; Hauschild et al., 2012; Sosman et al., 2012; McArthur et al., 2014]. Recently, a combination of anti-BRAF and anti-MEK agents has been associated with a higher response rate and longer DoR, as compared with anti-BRAF therapy alone [Larkin et al., 2014; Long et al., 2014]. The use of these targeted agents, however, is limited to those subjects who have a *BRAF* V600 mutation.

Despite new treatment options, there remains a substantial unmet need for treatments that extend survival and provide a better quality of life.

Nivolumab is a fully human immunoglobulin G (IgG)4 programmed death 1 (PD-1) immune-checkpoint inhibitor (CPI) antibody that blocks the interaction of the PD-1 receptor with its death ligands, thus disrupting the signal that blocks T-cell activation and proliferation [Wang et al., 2014]. In an open-label, randomized, Phase 3 study involving subjects with ipilimumab-refractory melanoma, nivolumab 240 mg intravenous (IV) every 2 weeks (Q2W) (n=268) was associated with a higher rate of objective response than chemotherapy (n=102) (32% vs. 11%). Median DoR for nivolumab was not reached, and for chemotherapy was 3.6 months [Weber et al., 2014].

When compared with dacarbazine in a Phase 3, randomized, double blind study in subjects with treatment-naive BRAF wild-type advanced melanoma (n=418), the median OS was not reached

for nivolumab vs 10.8 months for dacarbazine and 1-year survival rate was 72.9% vs. 42.1%, p<0.001, respectively. This survival advantage was observed in both programmed death-ligand 1 (PD-L1)-positive and -negative nivolumab-treated subjects. Nivolumab was also associated with improvements in progression-free survival (PFS) (5.1 vs. 2.2 months, p<0.001), and objective response rate (ORR) (40.0% vs. 13.9%, p<0.001). Common adverse events associated with nivolumab included fatigue (19.9%), pruritus (17%), and nausea (16.5%) [Robert et al., 2015a]. Nivolumab was approved for the treatment of unresectable or metastatic melanoma, as a single agent in subjects with disease progression following ipilimumab and (if BRAF V600 mutation positive) a BRAF inhibitor, and in combination with ipilimumab in subjects with BRAF V600 wild-type melanoma [OPDIVO®(nivolumab) USPI, 2020].

Another anti-PD-1 antibody, pembrolizumab, has been approved in the US on the basis of an ORR of 24% among subjects with advanced melanoma that progressed after ipilimumab, as well as treatment with a BRAF inhibitor if the subject had a *BRAF* V600 mutation [Keytruda®(pembrolizumab) USPI, 2020].

In an expansion cohort of a Phase 1 trial, subjects with ipilimumab refractory advanced melanoma were randomly assigned to pembrolizumab at 2 mg/kg every 3 weeks (Q3W) (n=89) or 10 mg/kg Q3W (n=84). The primary endpoint, ORR, was 26% in both groups. Treatment was well tolerated, with similar safety profiles in the 2 and 10 mg/kg groups and no drug-related deaths. The most common drug-related adverse events of any Grade were fatigue, pruritus, and rash [Robert et al., 2014]. Pembrolizumab provided significant improvements in PFS and durable objective responses while better preserving health-related quality of life compared with chemotherapy.

A Phase 3 study randomized 834 subjects with advanced melanoma in a 1:1:1 ratio to pembrolizumab (10 mg/kg) Q2W or Q3W or four doses of ipilimumab (3 mg/kg) Q3W. Primary endpoints were PFS and OS. Estimated 6-month PFS rates were 47.3% for pembrolizumab Q2W, 46.4% for pembrolizumab Q3W, and 26.5% for ipilimumab (hazard ratio [HR] 0.58, p<0.001). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively (HR 0.63; p=0.0005 for Q2W; HR 0.69; p=0.0036 for Q3W). Response rates were also improved with pembrolizumab as compared with ipilimumab. Treatment-related Grade 3 to 5 adverse events were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%) [Robert et al., 2015b]. Pembrolizumab received Food and Drug Administration (FDA) approval in September 2014 for subjects with melanoma previously treated with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Expansion cohorts of subjects with metastatic melanoma treated with MPDL3280A (anti-PD-L1 antibody, Roche) resulted in an ORR of 26% (9 out of 35) and a 24-week PFS of 35% [Hamid et al., 2013]. MPDL3280A is currently being explored in combination with vemurafenib in advanced BRAF-mutated melanoma.

The anti-PD-L1 antibody MEDI4736 is also currently under investigation in combination with dabrafenib and trametinib, or with trametinib alone, in subjects with metastatic melanoma with or without BRAF mutations, respectively.

1.1.1.2 Renal Cell Carcinoma (RCC)

Renal cell carcinoma (RCC) is the most common type of adult kidney cancer. The 5- and 10-year relative survival rates for kidney cancer are 73% and 63%, respectively [ACS, 2016]. It was estimated that in the US in 2016, 62,700 new cases of RCC would be diagnosed, and 14,240 deaths from kidney cancer would occur [ACS, 2016].

RCC is generally resistant to chemotherapy and radiation and has been treated with cytokines such as IL-2 or interferon-alfa, with limited success. Several targeted therapies are currently used to treat metastatic disease; including tyrosine kinase inhibitors (TKIs) such as sorafenib, sunitinib, pazopanib, and axitinib; mechanistic/mammalian target of rapamycin (mTOR) inhibitors such as temsirolimus and everolimus; and monoclonal antibody bevacizumab.

More recently, increased levels of PD-L1 were observed in RCC and kidney inflammation, thus it may be involved in reducing T-cell function [Ding et al., 2005]. Recent clinical trials appear to support this theory.

The initial experience with PD-L1 inhibitor MPDL3280A in RCC indicated the presence of responses across all doses, with some subjects with RCC experiencing prolonged stable disease (SD) before experiencing tumor response. The 24-week PFS was 50% among the 39 subjects evaluated for efficacy. A Phase 1b study showed that a combination with bevacizumab was well tolerated with promising preliminary clinical activity and immune modulation [Sznol et al., 2015]. MPDL3280A is currently being investigated as monotherapy and in combination with bevacizumab as compared with a control arm of sunitinib in subjects with treatment-naive, locally advanced or metastatic RCC. Nivolumab was tested in a randomized Phase 2 trial in subjects with advanced RCC, and long-lasting objective responses were reported in 20% to 22% of subjects, as well as median OS of 18.2 months or more [Motzer et al., 2015b]. A randomized open-label Phase 3 study comparing nivolumab to everolimus in previously treated advanced RCC has led to its registration for this indication. Subjects received nivolumab 3 mg/kg Q2W (n=406) or everolimus 10 mg daily (n=397). The median OS was 25.0 months with nivolumab and 19.6 months with everolimus, and the HR for death met the prespecified criterion for superiority ($p \leq 0.0148$). The ORR was greater with nivolumab than with everolimus, and the median PFS was similar. Grade 3 or 4 treatment-related adverse events occurred in 19% of the subjects receiving nivolumab and the most common event was fatigue in 2% of the subjects [Motzer et al., 2015a].

Nivolumab is also being developed in combination with sunitinib and pazopanib [Amin et al., 2014] as well as with the monoclonal antibody ipilimumab [Hammers et al., 2014].

A Phase 1 study of pembrolizumab with low-dose ipilimumab in subjects with advanced melanoma or RCC showed an acceptable safety profile. Pembrolizumab combinations are being further explored in a Phase 1/2 study with either pegylated interferon alfa-2b or ipilimumab in subjects with advanced melanoma and RCC.

Pembrolizumab is currently being investigated in a Phase 1/2 trial in combination with pazopanib in treatment-naive subjects with metastatic RCC. Once the recommended Phase 2 dose (RP2D) is determined, the potential for synergy by combining both agents will be evaluated.

1.1.1.3 Non-Small Cell Lung Cancer (NSCLC)

Lung cancer was the most frequently diagnosed cancer, accounting for about 13% of all cancer diagnoses in 2012. It also accounts for more deaths than any other cancer; the 1- and 5-year relative survival rates for lung cancer are 44% and 17%, respectively [Torre et al., 2015; ACS, 2016]. It was estimated that in the US in 2016, 224,390 new cases of lung cancer would be diagnosed, and 158,080 deaths from lung cancer would occur [ACS, 2016].

Subjects with advanced-stage non-small cell lung cancer (NSCLC) are usually treated in the first-line with chemotherapy (platinum, docetaxel, gemcitabine, paclitaxel, pemetrexed, and vinorelbine). Targeted therapies have been moving into first-line treatment, and these include anti-angiogenesis monoclonal antibodies (bevacizumab, ramucirumab), and TKIs against epidermal growth factor receptor (EGFR) (erlotinib, gefitinib, afatinib) and anaplastic lymphoma kinase (ALK) (crizotinib and ceritinib).

NSCLC has typically not been considered to be an immune-responsive tumor like RCC or melanoma and studies have shown that PD-L1 and programmed death-ligand 2 (PD-L2) are upregulated in NSCLC [Zou and Chen, 2008; Pardoll, 2012]. Another mechanism for immune resistance, especially among smokers, has been reported to be downregulation of the antigen-presenting machinery [Pleasance et al., 2010].

Anti-PD-1 activity in subjects with NSCLC was initially reported [Topalian et al., 2012], followed by the observation of disease stabilization and durable clinical responses (median DoR of 74 weeks and 1- and 2-year OS was 42% and 14% respectively) in both non-squamous and squamous cell lung carcinoma [Brahmer and Pardoll, 2013]. Pneumonitis (including Grade 3/4) has been observed, which may be related to PD-1 blockade-enhanced pulmonary inflammation. Following these encouraging results, nivolumab was developed in two Phase 3 clinical trials, which led to its approval by the US FDA.

Second-line treatment of subjects with non-squamous histology progressing after one prior platinum doublet-based chemotherapy regimen has been reported [Paz-Ares et al., 2015]. Subjects received nivolumab 3 mg/kg Q2W (n=292) or docetaxel 75 mg/m^2 Q3W (n=290). Nivolumab met the primary endpoint of superiority in OS, (HR=0.73; 96% confidence interval [CI]: 0.59, 0.89; p=0.00155). Also observed were improved ORR (19.2% vs 12.4%; p=0.0235) and modestly improved PFS (HR was 0.92; 95% CI: 0.77, 1.11; p=0.393). Nivolumab showed improved efficacy across all endpoints in subjects assessed as PD-L1-positive. Grade 3 to 5 drug-related adverse events (AEs) occurred in 10.5% (30/287) of nivolumab treated subjects, and no deaths were related to nivolumab.

Second-line treatment of 272 subjects with squamous cell histology progressing after one prior platinum-containing regimen has been reported [Brahmer et al., 2015]. Subjects received nivolumab 3 mg/kg Q2W or docetaxel 75 mg/m^2 Q3W. The median OS was 9.2 months (95% CI, 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel. The risk of death was 41% lower with nivolumab than with docetaxel (HR, 0.59; 95% CI, 0.44 to 0.79; p<0.001). At 1 year, the OS rate was 42% (95% CI, 34 to 50) with nivolumab versus 24% (95% CI, 17 to 31) with docetaxel. The objective response rate (ORR) was 20% with nivolumab versus 9% with docetaxel (p=0.008). The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR for death or disease progression, 0.62; p<0.001). Clinical benefit of nivolumab treatment did not strictly correlate with PD-L1 levels. Treatment-related AEs of

Grade 3 or 4 were reported in 7% of the subjects in the nivolumab group as compared with 55% of those in the docetaxel group. Nivolumab is now being studied in the neoadjuvant setting in NSCLC (NCT02259621).

Pembrolizumab has been studied in a multi-part Phase 1 clinical trial. Previously treated subjects with locally advanced or metastatic NSCLC were enrolled to a training group (n=182) or a validation group (n=313) and their PD-L1 status was assessed by an immunohistochemical assay. Subjects received pembrolizumab at a dose of either 2 mg/kg or 10 mg/kg Q3W or 10 mg/kg Q2W. Among all subjects, the ORR was 19.4%, and the median DoR was 12.5 months. The median PFS was 3.7 months, and the median OS was 12.0 months. Among subjects with a PD-L1 expression tumor proportion score (TPS) of at least 50% in the validation group, the ORR was 45.2%, median PFS was 6.3 months, and median OS was not reached. Treatment was generally well tolerated (common side effects attributed to pembrolizumab included fatigue, pruritus, and decreased appetite), although three subjects experienced Grade 3/4 drug-related pneumonitis [Garon et al., 2015]. Studies of pembrolizumab in the adjuvant (NCT02504372) and neoadjuvant settings in NSCLC (NCT02382406) are now recruiting.

Blocking PD-L1 is another strategy being evaluated in subjects with NSCLC. In previously treated subjects with metastatic NSCLC, an ORR of 24% (9 out of 37) was observed in subjects with both squamous and non-squamous histology treated with MPDL3280A. Several subjects had rapid tumor shrinkage and other subjects had delayed responses after apparent radiographic progression. Subjects with positive PD-L1 tumor status showed an ORR of 100% (4/4) and a progression (progressive disease [PD]) rate of 0% (0/4), while subjects with negative PD-L1 tumor status showed an ORR of 15% (4/26) and a PD rate of 58% (15/26). There was no Grade 3/4 pneumonitis, suggesting a potentially more tolerable safety profile with anti-PD-L1 inhibitors in subjects with NSCLC [Spigel et al., 2013]. Presently, MPDL3280A is being extensively studied, including in several ongoing Phase 3 studies in NSCLC.

Preliminary clinical activity has also been observed with MEDI4736 (tremelimumab, an anti-CTLA-4 monoclonal antibody) in subjects with NSCLC, among 13 subjects, three partial responses (PRs) and two minor responses were observed [Brahmer et al., 2014]. The safety profile was acceptable, with Grade 3/4 pneumonitis. Several studies of MEDI4736 in NSCLC are ongoing, including Phase 3 trials.

1.1.2 Histone Deacetylase (HDAC) and HDAC Inhibition

1.1.2.1 Histone Deacetylase (HDAC) as a Therapeutic Target in Cancer

Histone acetylation and deacetylation play important roles in the modulation of chromatin topology and the regulation of gene transcription. The histone deacetylase inhibitors (HDACi) inhibit the proliferation of tumor cells by inducing cell-cycle arrest, differentiation, and/or apoptosis in culture. Three classes of HDAC enzymes (I, IIa/IIb, and IV) utilize a zinc-catalyzed mechanism to deacetylate histones and non-histone proteins [Bolden et al., 2006; Minucci and Pelicci, 2006; Glaser, 2007; Rasheed et al., 2007; Rasheed et al., 2008; Haberland et al., 2009].

The activity of Class I HDACs (HDAC isoenzymes 1, 2, 3, and 8) is elevated in acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), non-Hodgkin's lymphoma (NHL), as well as prostate, gastric, colorectal, breast, and cervical cancers [Bolden et al., 2006; Nakagawa et al., 2007; Fritzsche et al., 2008; Weichert et al., 2008a; Weichert et al., 2008b].

Small interfering ribonucleic acid (siRNA)-mediated inhibition of HDAC 1 or 3 resulted in anti-proliferative effects, and HDAC2 inhibition using siRNA sensitized tumor cells to apoptosis [Bhaskara et al., 2008; Haberland et al., 2009].

Class IIb HDACs (HDAC isoenzymes 6 and 10) preferentially target non-histone proteins, such as α-tubulin and heat shock protein (HSP) 90. HSP90 has been shown to participate in malignant transformation by stabilizing oncoproteins such as Bcr-Abl, mutant Flt-3, AKT, c-Raf, estrogen receptors, Her-2, and vascular endothelial growth factor R (VEGF-R). Alpha-tubulin suppresses apoptosis in tumor cells by facilitating lysosomal clearance of misfolded proteins. Deacetylation of HSP90 and α-tubulin by HDAC6 or HDAC10 activates these proteins, contributing to the malignant phenotype. Conversely, inhibition of HDAC6 or HDAC10 has been shown to inhibit tumor growth. The synergy observed with the HSP90 inhibitor 17-AAG and the anti-tumor proteasome inhibitor bortezomib further support these proposed mechanisms [Glaser et al., 2004; Bali et al., 2005; Park et al., 2008; Rodriguez-Gonzalez et al., 2008; Schemies et al., 2009].

Several HDAC inhibitors have been approved by the FDA for the treatment of T-cell lymphoma, including vorinostat [Zolinza®(vorinostat) USPI, 2022] for the treatment of cutaneous manifestations in subjects with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease after two systemic therapies, romidepsin (ISTODAX®, Celgene Corporation, November 2009) for the treatment of CTCL and subsequently for peripheral T-cell lymphoma (PTCL), and belinostat (BELEODAC®, Spectrum Pharmaceuticals, Inc., July 2014) received accelerated approval from FDA for the treatment of subjects with relapsed or refractory PTCL. Panobinostat (FARYDAK®, Novartis Corporation, February 2015) was approved in combination with bortezomib and dexamethasone for the treatment of subjects with multiple myeloma. Several other HDACi are under clinical evaluation, including the following different classes: hydroxamic acid (e.g., resminostat, pracinostat, abexinostat, quisinostat), cyclic peptide (e.g., FK228/romidepsin), short-chain fatty acid (e.g., valproic acid), and benzamide (e.g., entinostat, mocetinostat, HBI-8000).

Preliminary results have suggested that HDACi are active in NSCLC and breast carcinoma when combined with other anti-tumor agents, however, their activity as single agent in solid tumors has not been demonstrated in clinical trials [Blumenschein et al., 2008; Crump et al., 2008; Luu et al., 2008; Modesitt et al., 2008; Vansteenkiste et al., 2008].

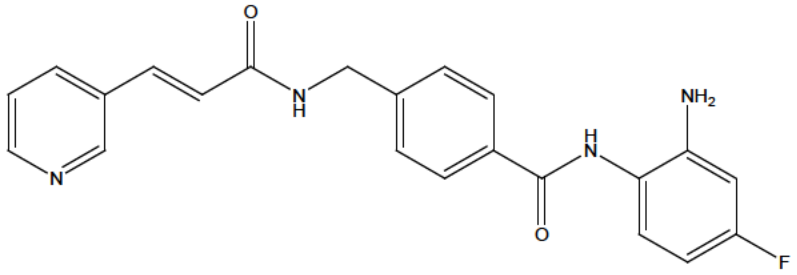
1.1.3 HBI-8000

1.1.3.1 HBI-8000 (CS055, chidamide)

HBI-8000 (CS055, chidamide), N-(2-Amino-4-fluorophenyl)-4-[N-[(E)-3-(3-pyridyl) acryloyl]aminomethyl] benzamide, is a member of the benzamide class of HDACi designed to block primarily the catalytic pocket of Class I HDACs. It was discovered by Shenzhen Chipscreen Biosciences Co., Ltd. (Chipscreen) in Shenzhen, China, using a computer-aided rational drug design [Yin et al., 2004]. It has been approved by China Food and Drug Administration (CFDA) for the treatment of relapsed or refractory PTCL in December 2014. It is now on the market under the trade name Epidaza in China. HUYABIO International, LLC (HUYABIO) has licensed worldwide rights (excluding China) of this compound. The development programs in solid tumors and hematologic malignancies are ongoing. The terms HBI-8000 will be used throughout this document.

The molecular and structural formulas for HBI-8000 are shown below.

Figure 1: Molecular and Structural Formulas for HBI-8000



HBI-8000 ($C_{22}H_{19}FN_4O_2$; molecular weight, 390.41)

HBI-8000 is an orally bioavailable, low-nanomolar inhibitor of cancer-associated HDAC enzymes with favorable pharmacology and safety profiles relative to existing benzamide and non-benzamide HDAC inhibitors. Please refer to the Investigator's Brochure (IB) for further information on HBI-8000 [IB v13.0, 2022].

1.1.3.2 Clinical Studies

To date, over 800 subjects have been dosed in the HBI-8000/chidamide clinical trials. It is estimated that chidamide has been prescribed to over 38,500 subjects in China since its conditional approval in December 2014 for the treatment of relapsed or refractory PTCL.

Twelve Phase 1, 1b, and Phase 2 clinical trials were completed in China and the US in subjects with solid tumors, NSCLC, PTCL, and CTCL, confirming a favorable safety and efficacy profile of HBI-8000. Two studies, Phase 1 and Phase 2 in NHL and NSCLC, are ongoing in Japan and China, respectively. Clinical trials with HBI-8000 have shown that HBI-8000 is generally well tolerated in subjects with advanced solid tumors or relapsed or refractory lymphoma at doses up to 32.5 mg 3 times a week (TIW) and 50 mg 2 times a week (BIW) (total weekly doses of approximately 100 mg in Phase 1 trials). The Phase 2 registration study in PTCL conducted in China demonstrated that 30 mg BIW was efficacious with an ORR of 28% (22/79) and a good safety profile. ORR was as high as 44% to 50% in some histological subtypes of PTCL [Shi et al., 2013; Shi et al., 2015].

Further information on HBI-8000 may be found in the IB [IB v13.0, 2022].

1.1.3.3 Clinical Pharmacology

Absorption

The single-dose pharmacokinetics (PK) of chidamide were evaluated in 33 subjects with T-cell lymphoma. After a single oral administration of 30 mg of chidamide after a meal, the average time to peak plasma drug concentration (T_{max}) was about 4 hours, average peak plasma drug concentration (C_{max}) was about 60 ng/mL, average area under curve from time 0 to the last measurable concentration (AUC_{0-t}) was about 660 ng×h/mL and the average endpoint elimination half-life was about 17 hours.

The multi-dose pharmacokinetic parameters of chidamide were evaluated in 19 T-cell lymphoma subjects administered with multiple doses of chidamide. Compared to that of single dose

subjects, the average AUC_{0-t} value increased 1.8-fold after the 8th dose, and the differences were statistically significant ($p<0.01$).

The effects of dose on pharmacokinetics were evaluated in 21 subjects with advanced stage solid tumor or lymphoma. A single dose of 25, 32.5, or 50 mg chidamide tablet was administered, the average AUC_{0-t} values were 809±390, 828±509, and 1120±438 ng×h/mL, respectively, indicating non-proportional increase of drug exposure versus the increasing dose, and possible dose saturation.

In 2021, a food effect study was completed following FDA guidelines. The results demonstrated that the administration of HBI-8000 with a high-fat meal had no impact on the extent of HBI-8000 exposure (area under the curve [AUC]) but reduced the C_{max} of HBI-8000 by approximately 24%. The variability of plasma PK parameters was similar when HBI-8000 was administered under fed and fasted condition. Therefore, it was concluded that timing of administration relative to meals would be unlikely to have a clinically significant effect on oral bioavailability.

It was observed during the clinical trial that drug administration after a meal might help alleviate potential gastrointestinal irritation caused by drug in some subjects. It is recommended to take the medication at least 30 minutes after a meal.

Distribution

The apparent volume of distribution (Vz/F) of chidamide is relatively large, indicating broad distribution in the human body. *In vitro* studies have shown that in human plasma, 89.1% to 99.3% of chidamide was protein-bound.

Metabolism and Excretion

Nuclear magnetic resonance (^{19}F NMR) and liquid chromatography-mass spectrometry (LC-MS/MS) were used to analyze the biological conversion and material balance in 4 subjects with T-cell lymphoma. Seven days after a single dose of 30 mg, 80.2%±9.5% of chidamide was excreted in urine and feces, the majority of which occurred within the first 72 hours. Chidamide was eliminated predominantly (67.6%±12.7%) through urine, and the remaining 12.6%±7.7% through feces. In the excreted chidamide, the parent drug form was 37.6%±9.2% of total dosage, of which 39.4% was through urine and 86.9% was through feces. There were also 5 main metabolites, products of mono-oxidation at different positions and hydrolysis of benzamide bond through two major metabolic pathways.

Further information on HBI-8000 may be found in the IB [IB v13.0, 2022].

1.2 Rationale for the Study

1.2.1 Rationale for the Use of HBI-8000 for the Treatment of Cancer

HBI-8000 inhibits several cancer-associated Class I (HDAC 1, 2, 3) and one Class IIb (HDAC10) HDACs in the nanomolar range and stimulates accumulation of acetylated histones H3 and H4 in tumor cells [Ning et al., 2012]. *In vitro*, HBI-8000 inhibits the growth of a wide variety of tumor cell lines, with 50% inhibitory concentrations (IC_{50}) in the single-digit micromolar range. HBI-8000 is non-toxic to non-transformed cells (IC_{50} ≥100 micromolar) [Ning et al., 2012]. *In vivo*, HBI-8000 has demonstrated dose-dependent anti-tumor activity

against human xenograft models [Ning et al., 2012]. Results from pre-clinical pharmacokinetic (PK) and toxicology studies in rats and dogs as well as results from a Phase 1 study conducted to date [Shenzhen Chipscreen Biosciences Co., 2008] suggest that HBI-8000 has favorable PK and safety profiles relative to other HDAC inhibitors.

1.2.2 Rationale for the Use of HDAC Inhibitors in Melanoma

Melanoma is the deadliest form of skin cancer, and its incidence has been increasing. Although immunogenic, melanoma is not effectively cleared by host immunity. The studies of the therapeutic, anti-melanoma potential of the HDACi by assessing both its cytotoxic effects on melanoma cells as well as enhancement of immune recognition of melanoma have demonstrated that HDACi exert a dual effect upon melanoma cells by affecting not only growth/survival but also by increasing melanoma immunogenicity [Boyle et al., 2005; Woods et al., 2013; Woods et al., 2015]. These effects provide a strong indication for future evaluation of HDACi in melanoma treatment [Woods et al., 2013].

HDACi are immunomodulatory, and demonstrate antitumor activity in various tumor models including malignant melanoma. Combination of HDACi and IL-2 increased anti-tumor effect in a melanoma model via activated cytotoxic T cells [Kato et al., 2014]. HDACi have shown remarkable anti-tumor activity, leading to FDA approval of several HDACi for the treatment of T-cell lymphoma and multiple myeloma. Several others are currently at various stages of clinical development for the treatment of hematological malignancies and solid tumors, including melanoma. It was shown that treatment with HDACi results in increased expression of pro-inflammatory surface markers on melanoma cells, increased surface expression of major histocompatibility complex (MHC), CD40, and CD80 and perhaps CD86, thus increasing the immunogenicity of melanoma cells and promoting enhanced T-cell activation [Dokmanovic et al., 2007; Woods et al., 2013; Woods et al., 2015]. These results indicate that HDAC inhibitors are a potentially useful class of compounds for elucidating cell signaling pathways and for developing new approaches to the treatment of melanoma [Boyle et al., 2005]. Recent clinical trial data have shown that blockade of the PD-1/PD-L1 interaction is effective in the treatment of melanoma, renal cell and non-small cell lung cancer [Topalian et al., 2012; Topalian et al., 2014]. Importantly, responses to PD-1 blocking antibodies were preferentially seen in subjects with tumors expressing PD-L1, and HDACi targeting Class I HDACs, but not Class II, augmented expression of PD-L1 in melanoma cells [Woods et al., 2013; Woods et al., 2015]. In addition, increased expression of PD-L1 is dependent on inhibition of multiple Class I HDACs. Class I HDAC inhibition upregulates PD-1 ligands in melanoma and increases the efficacy of PD-1 blockade [Topalian et al., 2014]. In *in vivo* experiments combining HDACi treatment of melanoma bearing mice with anti-PD-L1 antibodies, mice receiving the combination treatment had a survival advantage over those receiving PD-L1 blocking antibodies or HDACi alone [Woods et al., 2014]. It was also shown that HDACi sensitize apoptosis resistant melanomas to human cytotoxic T lymphocytes through regulation of TRAIL/DR5 pathway [Jazirehi et al., 2014; Balliu et al., 2015]. HDACs are acting as mediators of resistance to apoptosis in melanoma and as targets for combination therapy with selective BRAF inhibitors; co-targeting histone deacetylases and oncogenic BRAF synergistically kills human melanoma cells by necrosis [Lai et al., 2012; Lai et al., 2013]. These results provide a scientific rationale for the evaluation of combination therapies with HDAC inhibitors in melanoma.

1.2.3 Rationale for the Use of HDAC Inhibitors in Renal Cell Carcinoma

All the members of the Class I subfamily of HDACs are deregulated in many cancers. Several studies have reported high expression of HDAC1, HDAC2 and HDAC3 in RCC, colorectal and gastric cancers as well as in Hodgkin's lymphoma [Fritzsche et al., 2008; Weichert et al., 2008c; Adams et al., 2010].

The critical role that HDACs play in cancer progression has been widely appreciated, since changes in HDAC expression or inappropriate recruitment of these enzymes has been observed in a number of human cancers [Marks and Breslow, 2007]. Class I HDACs, specifically HDACs 1 and 2, are highly expressed in RCC, making these particularly interesting therapeutic targets [Fritzsche et al., 2008]. Because of this, researchers have focused much of their efforts on designing effective treatments to inhibit HDACs [Epping and Bernards, 2009; Mund and Lyko, 2010]. HDACi have been shown to induce growth arrest, apoptosis, and differentiation in a number of tumor cell lines as well as in mouse tumor models. They are also important for inhibiting tumor angiogenesis, which is normally critical for growth and progression of solid tumors [Liu et al., 2006; Marks, 2010].

In RCC, HDACs play an important role in promoting both cell cycle arrest and apoptosis. Treatment of RCC cell lines with valproic acid (VPA) inhibits proliferation and results in increased levels of p21, a cyclin-dependent kinase inhibitor [Jones et al., 2009]. While HDACi have been touted for their ability to promote G_1 arrest, primarily through the up-regulation of p21 [Marks and Breslow, 2007], these small molecules are also capable of inducing arrest at the G_2-M transition [Epping and Bernards, 2009]. This G_2-M arrest has been documented in RCC cell lines treated with the HDACi LBH589 (panobinostat) as well as the novel γ–lactam-based HDACi KBH-A145 [Cha et al., 2009; Kwon et al., 2009]. Mechanistically, LBH589 treatment reduces the protein levels of both Aurora A and B kinases, which normally play important roles during mitosis, and this effect is mediated specifically through the inhibition of HDAC3 and HDAC6 [Cha et al., 2009]. Since the levels of both Aurora A and B kinases are significantly higher in tumors taken from RCC subjects, the use of HDACi as potential therapies for RCC is certainly supported.

Currently, it appears that combinatorial therapy involving HDACs holds the most promise for treating RCC, and there have been a number of studies utilizing this approach [Stadler et al., 2006; Hainsworth et al., 2011; Su et al., 2011; Pili et al., 2012; Dasari et al., 2013]. First, combinatorial therapy enhances anti-proliferative effects. VPA, in combination with low-dosed interferon-α, is more effective at reducing overall HDAC activity as well as inhibiting cell proliferation in RCC cell lines compared with single-agent treatments [Jones et al., 2009]. Additionally, this combinatorial effect is seen when VPA is used in conjunction with AEE788, a receptor TKI, or RAD001, an inhibitor of mTOR [Juengel et al., 2010; Juengel et al., 2012]. Likewise, the combination of suberoylanilide hydroxamine (SAHA) with either the protease inhibitor ritonavir or the topoisomerase I inhibitor topotecan results in more potent inhibition of HDACs, promotion of pRb dephosphorylation, and reduced proliferation in renal cancer cells [Sato et al., 2010; Sato et al., 2011].

Second, combination therapy involving HDACs appears to attenuate the levels of hypoxia inducible factors (HIFs) which are often dysregulated in clear cell RCC due to the inactivation of the tumor suppressor gene, von Hippel-Lindau (VHL) [Cheng et al., 2009]. This effect can be augmented when HDAC, particularly LBH589, are used in conjunction with rapamycin, an

inhibitor of the mTOR [Verheul et al., 2008]. Since HIFs are pro-angiogenic transcription factors that support tumor growth by promoting vascularization, these studies not only implicate HDAC involvement in the upregulation of HIFs during tumor growth, but they also suggest a role for HDACs in RCC treatment.

Finally, HDACs have been used in combination with retinoic acid (RA) to promote cancer cell differentiation, which is compromised during cancer development and serves as a hallmark of the disease [Epping and Bernards, 2009]. RA is a diffusible factor derived from vitamin A that has been used for the treatment of several cancers. However, some renal malignancies have shown resistance to this therapy [Berg et al., 1997; Altucci and Gronemeyer, 2001]. Data from RCC cell lines suggest that this retinoid-resistance is due to loss of *RARβ2* expression [Wang et al., 2005]. Treatment with MS-275 (entinostat) results in hyperacetylation of the *RARβ2* promoter and re-expression of this gene, restoring sensitivity of these lines to retinoids. When MS-275 is combined with 13-*cis*-retinoic acid (cRA), there is a significant inhibition of RCC tumor growth in mouse xenografts. Similar results have been obtained with TSA and all-*trans* retinoic acid [Touma et al., 2005]. This combinatorial treatment of HDACi and cRA has been used in Phase 1 clinical trials for subjects with advanced solid tumors, including renal malignancies [Pili et al., 2012]. Taken together, these data suggest the HDAC inhibition coupled with additional therapies may be an effective method of treatment for RCC.

1.2.4 Rationale for the Use of HDAC Inhibitors in NSCLC

Three HDAC inhibitors have clinically proven antitumor activity and were approved by FDA for the treatment of peripheral/cutaneous T-cell lymphoma, [Duvic et al., 2007; Olsen et al., 2007; Piekarz et al., 2009; Piekarz et al., 2011] and the utility of HDAC inhibition in the treatment of other cancers such as NSCLC is very promising. A randomized Phase 2 trial in NSCLC showed improved response rates when HDACi vorinostat was added to first-line carboplatin and paclitaxel [Ramalingam et al., 2010]. Current research on incorporating HDAC inhibitors into NSCLC treatment includes also their use in combination with EGFR TKIs.

The EGFR TKI erlotinib is a standard treatment for NSCLC and has particularly striking activity against tumors with *EGFR* mutations [Lynch et al., 2004; Paez et al., 2004; Pao et al., 2004]. Multiple lines of preclinical evidence suggest a complex interplay between the sensitivity of NSCLCs to EGFR TKIs, HDAC inhibitors, and the epithelial-mesenchymal transition (EMT) state [Thomson et al., 2005; Yauch et al., 2005; Witta et al., 2006; Thiery et al., 2009]. Cells with a mesenchymal phenotype, characterized by high vimentin and ZEB1 transcription factor activity, can be resensitized to EGFR TKIs with HDAC inhibitors, particularly entinostat, which is thought to cause reversion to an epithelial phenotype [Witta et al., 2006].

The results of clinical trials [Witta et al., 2012] suggest that HDAC inhibitors can preserve a pre-existing epithelial phenotype and that such subjects will demonstrate sensitivity to erlotinib for a longer period of time. Treatment with various HDAC inhibitors restores expression of Tumor growth factor β (TGF-β) type II receptor, resensitizing cells to TGF-β-mediated cell death [Halder et al., 2011].

A potentially complementary mechanism of reversible drug tolerance was recently reported in *EGFR* mutation-positive cancers. Concomitant treatment of EGFR TKIs with HDAC inhibitors prevented formation of drug-tolerant cells, potentially by reducing the activity of an HDAC [Sharma et al., 2010].

These data suggest that there are multiple pathways by which HDAC inhibition may both potentiate and prolong the antitumor effect of targeted treatment in NSCLC [Kim et al., 2007].

HBI-8000 is a selective inhibitor of Class I HDACs 1, 2, and 3 and Class IIb HDAC10. All the members of the Class I subfamily of HDACs are deregulated in many cancers. In several studies analyzing subject cancer samples, overexpression of HDAC1 has been found in lung, gastric, breast, pancreatic, hepatocellular, and prostate carcinomas and in most of the cases HDAC1 up-regulation associates with poor prognosis [Choi et al., 2001; Zhang et al., 2005; Choi et al., 2010; Minamiya et al., 2011]. These studies point to overexpression of Class I HDACs, in particular HDAC1, as a cancer marker associated with poor prognosis.

In vitro studies also show that HBI-8000 could sensitize NSCLC cells to deoxyribonucleic acid (DNA) damage induced by carboplatin at clinically relevant concentration, consistent with other reports that suggest the pivotal roles of HDACs in DNA damage and autophagy [Robert et al., 2011b; Botrugno et al., 2012].

HBI-8000 in combination with carboplatin strongly induces the phosphorylation of histone H2A.X (gH2A.X), a hallmark of the DNA damage response, increases cell cycle arrest at G2/M, and increases apoptotic cell death in NSCLC cell lines A549 and NCI–H157 at a non-cytotoxic concentration of 0.3 mM [Zhou et al., 2014]. Several reports revealed an epigenetic regulatory component in the reversible process of EMT [Kiesslich et al., 2013; Pattabiraman and Weinberg, 2014]. It was shown that chidamide can repress EMT and consequent drug resistance induced by TGFβ on the NSCLC cell line NCI-H292. *In vitro*, TGFβ downregulated the expression of the epithelial marker E-cadherin and upregulated the expression of the mesenchymal markers N-cadherin and vimentin, resulting in less growth inhibition by carboplatin treatment in the NSCLC cell line NCI-H292, a cellular model for the EMT process [Shintani et al., 2011]. In this experimental model, adding a noncytotoxic concentration of HBI-8000 to the cultured H292 cells antagonized the above-mentioned effect by repressing the induction of N-cadherin and restoring the carboplatin-induced growth inhibition in this cell line.

Emerging data suggest that there are three major mechanisms underlying the anti-cancer activities of HDAC inhibitors: i) preferential induction of growth arrest and apoptosis in blood and lymphoid-derived tumor cells, ii) activation of natural killer (NK)-mediated and CD8+ cytotoxic T lymphocyte (CTL)-mediated antigen-specific cellular antitumor immunity, and iii) partial reversal of EMT and drug resistance of tumor cells. However, the activation of NK- and antigen-specific CTL-mediated cellular antitumor immunity appears only to be associated with the benzamide type of selective HDAC inhibitors such as HBI-8000.

This immunomodulatory mechanism of action of HBI-8000 strongly suggest that HBI-8000 is a very promising candidate for use in combination with immune CPIs such as nivolumab, approved for the treatment of lung cancer.

1.2.5 Rationale for Using HBI-8000 with Checkpoint Inhibitors (CPIs)

The unique aspects of HDAC inhibition that contribute to anti-cancer activity have been described, e.g., reprogramming distorted transcription patterns and signal pathways in tumor cells, and modulation of the tumor microenvironment and immune system [Minucci and Pelicci, 2006; Haberland et al., 2009]. For instance, benzamides induce MHC Class I-like antigens (e.g., MHC Class I chain-related proteins A and B [MICA and MICB]) and the ligand of the natural

killer receptor (natural-killer group 2, member D [NKG2D]), which can stimulate innate anti-tumor immunity [Schmudde et al., 2008]. Similar effects were observed with HBI-8000 on in vitro cell lines and in clinical samples [Dong et al., 2012; Ning et al., 2012]. HBI-8000 enhances the cytotoxic effects of human peripheral mononuclear cells *ex vivo* on K562 target cells via upregulation of proteins involved in NK cell functions (e.g., NKG2D and granzymes) that lead to the activation of NK cells. This NK activity was also observed in peripheral white blood cells derived from two lymphoma subjects who responded to chidamide administration [Dong et al., 2012; Ning et al., 2012].

It has been reported that HBI-8000 induces expression of the leukemia-specific preferentially expressed antigen in melanoma (PRAME) in both cell lines and leukemia blasts in bone marrow samples from subjects, resulting in increased PRAME specific- and CTL-mediated *in vitro* cytotoxicity against leukemia [Yao et al., 2013]. Most importantly, the pharmacological concentrations required to activate either NK-mediated or antigen specific CTL activities by HBI-8000 *in vitro, ex vivo*, and in subjects were between 100 and 500 nM, a concentration where cytotoxicity against normal cells was not evident. Inhibition of different subtypes of HDAC could have distinct effects on regulatory T cell (Treg) activity. For example, inhibition of Class II or IV subtypes 6, 9, and 11 may exaggerate Treg expansion while inhibition of Class I subtypes 1, 2, and 3 may repress the Treg expansion, which in general favors the anti-tumor immune response by Class I selective inhibitors [Wang et al., 2009; Beier et al., 2012; Shen and Pili, 2012].

1.2.6 Rationale for HBI-8000 Combined with CPI Therapy in CPI-Relapsed or Refractory Malignancies

Despite recent successes of CPI therapies in multiple tumor types as evidenced by an increase in ORR and prolonged PFS, disease relapse and treatment failure are still being observed in advanced cancer subjects. There are many mechanisms for acquired resistance to CPI therapies. As an HDACi and epigenetic modulator, HBI-8000 has the potential to address and overcome some of these resistance mechanisms. These include mechanisms based on MHC Class I silencing, Treg and myeloid-derived suppressor cell (MDSC) expansion and activity, T cell exhaustion, poor NK and NK T cell activity, and inadequate response to interferonγ signaling in tumor microenvironment.

In animal models HBI-8000, when combined with CPI (PD-1 or PD-L1 antibody) was statistically superior to either single agent to suppress tumor growth and to prolong animal survival (unpublished). The data suggest that the presence of HBI-8000 can either overcome innate resistance or prevent acquired resistance, or both.

Furthermore, preclinical data from a unique model of CPI failure/resistance developed by HUYABIO has shown that mice bearing MC38 tumors that are failing to respond or have developed resistance to one CPI treatment (PD-1 or PD-L1 Ab) can be rescued by HBI-8000 combined with the reciprocal CPI. These data suggest that HBI-8000 combined with CPI may rescue subjects that have relapsed or are refractory to the CPI therapy. In summary, emerging data suggest that there are three major mechanisms underlying the anti-cancer activities of HDACi: i) preferential induction of growth arrest and apoptosis in blood and lymphoid-derived tumor cells, ii) activation of NK-mediated and CD8+ CTL-mediated antigen-specific cellular anti-tumor immunity, and iii) partial reversal of EMT and drug resistance of tumor cells as

described in Figure 2. However, the activation of NK- and antigen-specific CTL-mediated cellular anti-tumor immunity appears only to be associated with the benzamide type of selective HDACi such as HBI-8000 (Figure 2).

Figure 2: Proposed Manifold Anti-Tumor Mechanisms of Chidamide (HBI-8000)

Immunomodulatory effects of HBI-8000 such as activation of NK- and CD8 T-cell-mediated antitumor activity makes this HDAC inhibitor an attractive candidate for the combination therapy with immune checkpoint inhibitors, such as anti-PD-1 antibodies.

1.2.7 Effects of HDACi on Immune Checkpoint Biomarkers

Recently, HDAC inhibition has been shown to upregulate PD-1 ligand in melanoma and thereby augmenting immunotherapy with PD-1 blockade [Woods et al., 2015]. Class I HDACi upregulate the expression of PD-L1 and to a lesser extent PD-L2 in human and murine melanoma cell lines and in subject tumors. The upregulation of PD ligands was durable and lasted beyond 96 hours. These results suggest that combination of Class I HDACi such as HBI-8000 may have activity in combination with PD-1 blockade antibodies. Testing PD-1 blockade with HBI-8000 is therefore of considerable interest.

1.2.8 Effects of HDAC10 Inhibition

Specific inhibition of HDAC10 or HDAC6 has been shown to reduce expression of VEGF-R1 and VEGF-R2 in tumor cells, presumably via enhancement of HSP90 acetylation [Park et al., 2008]. Autophagy is implicated in tumor resistance to multiple anti-cancer agents, and HDAC10 activity has been shown to promote the autophagy-mediated survival response to several anti-cancer agents [Oehme et al., 2013]. Inhibition of HDAC10 reduces the autophagic response to cytotoxic agents.

1.2.9 Immunomodulatory Mechanisms Integrate with Cancer Cell Intrinsic Mechanisms of Cell Killing by HDACi

The current dominant dogma is that cancer is caused by genetic defects: gene mutations, abnormal gene expression and epigenetic dysregulation, which occur in cancer cells but these mechanisms are not limited to cancer cells and affect immunocyte function as well. Some of these cancer cell intrinsic defects are reversible and the promise of epigenetic regulators like HDACi is that they can concurrently target multiple aberrant or compensatory signaling pathways found in cancer cells by restoring the genome, and by extension the transcriptome, to a more normal-like state. HBI-8000 causes modulation of gene regulation patterns that is consistent with that hypothesis. Genes in several functional clusters were regulated by HBI-8000 [Ning et al., 2012; Pan et al., 2014], including several genes important for cell cycle (CCNA2/Cyclin A2, CCNB2/Cyclin B2, CCNE2/Cyclin E2, CDKN1A/p21/WAF1, CHEK1/checkpoint kinase 1), apoptosis (DR6/ TNFRSF21/death receptor 6) and the response to antitumor therapies (ABCB10, ABCC2/MRP2, RAD23B, UBCH10/ubiquitin-conjugating enzyme E2C). HBI-8000 also regulated genes promoting epithelial differentiation (CDH1, KRT8) and reducing the epithelial-to-mesenchyme transition, an important process in tumor invasion and metastasis (CDH2/N-cadherin). While these HDACi effects on the cancer cell are important, the effects of HDACi are not limited to regulation of cell cycle, cell differentiation and cell death, but also affect immune recognition through effects on the cancer cell and immunocytes.

Notably, HDAC inhibitors also increase tumor cell ligands promoting NK cell-mediated tumor cell lysis and NK cell NKG2D expression involved in tumor cell lysis, thereby promoting tumor immunocyte cross talk involved in immune surveillance. For example, in pancreatic cancer valproate treatment, which inhibits HDAC Classes 1 and 2 (but not 6 and 10) upregulates NKG2D ligands major histocompatibility complex Class I-related chain A and B (MICA and MICB) in pancreatic cancer cells increasing susceptibility of NK cell-mediated cancer cell lysis in vitro and in vivo [Shi et al., 2014]. HDAC inhibition by entinostat is also associated with enhanced NK cell cytotoxicity against colon carcinoma and NK cells associated with increase in MHC Class I-related Chains (MIC) expression in tumor cells and NKG2D in primary human NK cells [Zhu et al., 2015].

1.2.10 Hypothesis

The HDACi are a new class of cytostatic agents that inhibit the proliferation of tumor cells in culture and *in vivo* by inducing cell cycle arrest, differentiation and/or apoptosis. Histone acetylation and deacetylation play important roles in the modulation of chromatin topology and the regulation of gene transcription.

HBI-8000 inhibits several cancer-associated Class I and one Class IIb HDACs in the nanomolar range and stimulates accumulation of acetylated histones H3 and H4 in tumor cells. IC_{50} values for these enzymes ranged from 67 to 160 nM, similar to vorinostat and more potent than SNDX-275 (MS275, entinostat, Syndax) in side-by-side comparison and more potent than the published values for MGCD0103 [Hess-Stumpp et al., 2007; Fournel et al., 2008].

In vitro, HBI-8000 inhibits the growth of a wide variety of tumor cell lines, with IC_{50} values in the single-digit micromolar range. *In vivo*, HBI-8000 has demonstrated dose-dependent

antitumor activity against a panel of mouse and human xenograft models, producing 60% to 84% inhibition of tumor growth at doses that did not cause weight loss or any overt signs of toxicity.

There are three distinct mechanisms of action associated with HBI-8000, i) a direct anti-tumor mechanisms and modulation of cancer cell, ii) intrinsic epigenetic regulation, and iii) an immunomodulatory mechanism as illustrated in Figure 2.

Findings support the hypothesis that HBI-8000 will play a role in immunocyte activation due to its inhibition of HDAC 1, 2, 3 and 10 in those cells (see Figure 2) [Muraro et al., 2015; Salgado et al., 2015].

These results suggest that combination of Class I HDACi such as HBI-8000 may have activity in combination with PD-1 blockade antibodies.

1.2.11 Risk-Benefit Assessment

In clinical studies, treatment with HBI-8000 has been associated with exposure-related Grade 1 to 3 myelosuppression, including thrombocytopenia, anemia, and neutropenia or leukopenia. One case of Grade 4 thrombocytopenia has been reported to date in ongoing Phase 2 trials. When hematologic AEs of Grade 3 or higher occur, symptomatic treatment should be provided, and dosing should be suspended until such hematologic AEs recover to acceptable levels, as monitored by routine blood tests.

In a Phase 2 Study TG0902CDM, of 10 subjects who had a prolonged QT interval corrected for heart rate (QTc interval) during HBI-8000 treatment, the event was Grade 1 in eight subjects, and one subject each had a Grade 2 and Grade 3 abnormality. In most subjects, the QTc interval returned to normal following cessation of HBI-8000 treatment.

Patients in Phase 1b (Part 1) of this study received a 20 mg, 30 mg, or 40 mg of HBI-8000 once daily starting on Cycle 1 Day 1 (C1D1). Concomitant administration of nivolumab was started only on Cycle 1 Day 2, after the last PK sample was collected for HBI-8000 administered on C1D1. Patients had PK blood samples and triplicate digital 12-lead Holter electrocardiograms (ECGs) collected on Baseline Day (ECG only) and on C1D1 (both PK and ECG).

No changes of interest were observed in mean or median change in heart rate (ΔHR) (ventricular heart rate) in any dose group over the 0 to 4 hour interval on C1D1, indicating that QTc using Fridericia's correction formula (QTcF) was unlikely to be confounded by changes in HR. This was supported by the scatter plot of individual patient log QTcF versus log RR interval values, which showed no statistically significant relationship (p=0.1588) or unidirectional trend between these ECG intervals.

QTcF data were available for 1 of 3 patients in the 20 mg dose group, 6 of 6 patients in the 30 mg dose group, and 7 of 7 patients in the 40 mg dose group (two patients in the 20 mg dose group had left or right bundle branch block which precluded estimation of QT values; consequently, QTcF data were available for only 1 of the 3 patients in this dose group).

Mean and median ΔQTcF showed no discernible change in the 30 mg dose group and a decrease in the 40 mg dose group on C1D1. Mean ΔQTcF on C1D1 showed no relationship (30 mg dose) or an inverse relationship (40 mg dose) with time and mean HBI-8000 mean concentrations. Similar results were observed for individual patients, with the majority showing no change or a decrease in ΔQTcF with increasing HBI-8000 concentrations. No QTcF values were >450 msec

and no ΔQTcF values were >30 msec. The 12-lead Holter ECG results and the results of CQT modeling show no prolongation of QTcF by HBI-8000 over the 20 to 40 mg dose range. Eight subjects receiving HBI-8000 in Study TG0902CDM had mild/trace pericardial effusion detected by cardiac ultrasound, but the subjects had no clinical symptoms. As pericardial effusion is one of the most common symptoms in advanced cancer, no definitive conclusions could be drawn regarding the relationship between the pericardial effusion and treatment with HBI-8000.

Results from preclinical PK and toxicology studies in rats and dogs, as well as results from Phase 1 safety studies in subjects with solid tumors and hematological malignancies, show that HBI-8000 has favorable PK and safety profiles, allowing twice weekly dosing.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of HBI-8000 when combined with a standard dose and regimen of nivolumab, to determine a 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 of the study 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 pharmacokinetics of twice weekly HBI-8000 when administered alone and in combination with nivolumab administered once every two weeks (Phase 1b all sites) and under applicable manufacturer dosing information (Phase 2 selected sites)
- To characterize the effect of HBI-8000 on the electrocardiogram QT interval corrected for heart rate (QTc interval) (Phase 1b)

2.3 Exploratory Objectives

The exploratory objectives of the study 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 Criteria for Evaluation

Safety Endpoints:

Safety and tolerability of HBI-8000 when combined with standard dose and regimen of nivolumab will be measured by the number of subjects with AEs and severity of AEs as defined by Common Terminology Criteria for Adverse Events (CTCAE) v4.03. AEs and dose-limiting toxicities (DLTs) reported by the subjects or observed during physical examination, vital signs assessments, ECGs, and laboratory tests results will be recorded and assessed by severity and association with study treatment. Eastern Cooperative Oncology Group (ECOG) performance status will be monitored.

Efficacy Endpoints:

Target lesion(s) and non-target lesion(s) will be assessed by imaging studies at screening for baseline assessment, in the last week of Cycle 2 including C3D1, and every 8 weeks (±3 days) thereafter during study treatment according to guidelines specified in Response Evaluation

Criteria in Solid Tumors (RECIST) version 1.1 and Immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) (Appendix 7). The following parameters will be obtained:

- Objective Response (CR+PR) Rate (ORR)
- Disease Control (CR+PR+SD) Rate (DCR)
- Clinical Benefit (CR, PR, and if SD ≥12 weeks) Rate (CBR)
- Duration of Response (DoR)
- Progression-Free Survival (PFS)

Pharmacokinetic Characterization:

All subjects in Phase 1b and subjects at selected sites in Phase 2 will have the opportunity to participate in the population PK (POPK) analysis for HBI-8000. A sparse sampling schema will be applied (see Section 6.3, Appendix 2 and Appendix 3).

QTc Sub-Study:

In conjunction with POPK analysis, a QTc sub-study will be performed at specified time points in all subjects in Phase 1b (see Section 6.4, Appendix 2). At these time points, 12-lead Holter ECG measurements in triplicate will be obtained and reviewed by a central laboratory.

3 INVESTIGATIONAL PLAN

3.1 Study Design Overview

This is a multicenter Phase 1b/2, open-label, dose-finding study of HBI-8000 in combination with a fixed dose of nivolumab in the US. In the Phase 1b dose-escalation portion of the study up to 18 subjects with melanoma, RCC, or NSCLC will be enrolled to receive HBI-8000 orally twice weekly. The starting dose will be 20 mg, then escalated to 30 mg and 40 mg pending safety. The standard dose of nivolumab will be applied. In the event that an MTD is not reached, 40 mg will be the RP2D for HBI-8000.

In the Phase 2 portion of the study, subjects with melanoma and NSCLC who have been treated with checkpoint inhibitor(s) (CPI) will also be evaluated in addition to CPI-naïve melanoma and NSCLC subjects. Up to 20 subjects will be enrolled in each population, and up to 40 will be enrolled in CPI-naïve melanoma cohort to allow correlative sub-studies. Treatment will continue until disease progression or unacceptable toxicity. Subjects with RCC will not be included in Phase 2. Subjects with NSCLC will not be enrolled under Protocol Amendment 5. 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).

The study will include a screening period, study treatment until disease progression or unacceptable toxicity, End-of-Treatment (EoT) safety follow-up, and follow-up for progression-free survival (and disease progression if not already recorded). For the Phase 1b dose-escalation portion, the estimated accrual duration is 6 to 12 months and for the Phase 2 cohort expansion portion it is 24 to 36 months.

With Protocol Amendment 7, subjects with clinical benefit at the time of the data cut-off for the main study will be entered in the Extension Phase of the study to continue HBI-8000 treatment and be monitored for safety until the earliest occurrence of disease progression, unacceptable toxicities, initiation of another anti-cancer treatment, referral to hospice, discretion of the investigator or consent withdrawal.

The Schedule of Dosing and Assessments is presented in Appendix 1.

3.2 Study Treatment

Each treatment cycle consists of 28 consecutive days. HBI-8000 will be administered orally, approximately 30 minutes after a meal, twice a week with 3 to 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). 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.

If HBI-8000 administration is delayed or interrupted, administration of nivolumab will not be affected. A cycle is 28 consecutive days irrespective of administration of either HBI-8000 or nivolumab.

3.2.1 Dose Escalation Schema

Eligible subjects will be enrolled sequentially from Dose Level 1 (DL1) escalating through DL3 in a 3+3 design. At DL1 (20 mg), 3 subjects will be enrolled initially. If no subject experiences a DLT, the dose will be escalated to DL2 (30 mg). If one of the first 3 subjects experiences a DLT, 3 additional subjects will be accrued at DL1. If only 1 of the 6 subjects enrolled in DL1 experiences a DLT, the dose will be escalated to DL2 (30 mg). If ≥2 subjects experience DLT at DL1, that dose level will be deemed to exceed the MTD. In that case, the dose will be reduced to 50% of the starting dose (DL−1: 10 mg) in the next dose cohort. If either DL2 or DL3 is deemed to exceed the MTD, subsequent subjects will be enrolled to DL1 or DL2, respectively, to assure tolerability at the previous dose level.

The MTD is defined as the dose at which DLT is observed in no more than 1 of 6 subjects during the first 4 weeks of treatment. For a given dose level, enrollment of up to 6 subjects is allowed as needed to assure that no more than 1 of 6 subjects experiences DLT. This process will be repeated up to DL3 (40 mg). At DL3, a minimum of 6 subjects will be evaluated. If no more than 1 of 6 subjects treated at DL3 experience DLT, DL3 will be selected for efficacy evaluation in the cohort extension part of this study.

There will be no intra-subject dose escalation.

Table 1: Dose Level Designation

Dose Level (DL)	HBI-8000 Dose (mg)	Frequency
−2	10	Once a week
−1	10	Twice a week
1	20	Twice a week
2	30	Twice a week
3	40	Twice a week

Within a dose level, the 1st subject must receive a minimum of 2 doses of HBI-8000 before additional subjects are enrolled. Escalation to the next dose cohort must not occur until all of the following conditions are met:

- All subjects in the current dose cohort must complete the 1st treatment cycle
- All subjects in the current dose cohort are able to begin Cycle 2 within 14 days of the planned start – any subject unable to receive Cycle 2 for reasons other than toxicity will be replaced

The decision to escalate to the next dose level will be made following review of all relevant safety information, including AEs, and clinical laboratory test results. The decision to escalate will be made jointly by the Sponsor, contract research organization (CRO) and the Investigators.

3.2.2 Cohort Expansion

Phase 2 of the study will begin after the RP2D of HBI-8000 is identified for use in combination with nivolumab. Up to approximately 20 subjects for each of the following indications will be enrolled: NSCLC CPI-treated, NSCLC CPI-naive, melanoma CPI-treated. In addition, up to 40 CPI-naïve subjects for the melanoma indication will be enrolled. These subjects will be treated at the RP2D, including subjects who received this dose in the dose-escalation portion. Subjects with NSCLC will not be enrolled under Protocol Amendment 5. 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).

3.2.3 Extension Phase

With Protocol Amendment 7, subjects with clinical benefit at the time of the data cut-off for the main study will be entered in the Extension Phase of the study to continue HBI-8000 treatment and be monitored for safety until the earliest occurrence of disease progression, unacceptable toxicities, initiation of another anti-cancer treatment, referral to hospice, discretion of the investigator or consent withdrawal.

3.2.4 Dose-Limiting Toxicity (DLT)

A DLT is defined as the following 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.

A. Hepatic Non-Hematologic DLT

Any one of the following events will be considered a hepatic DLT (irrespective of whether it is considered to be an immune-related adverse event [irAE]):

- Isolated Grade 4 aspartate aminotransferase (AST)/alanine aminotransferase (ALT)
- Isolated Grade 3 AST/ALT that fails to return to Grade 1 or less within 5 days
- Isolated Total Bilirubin ≥Grade 3
- AST or ALT >3 x upper limit of normal (ULN) AND concurrent total bilirubin >2 x ULN

B. Non-Hepatic Non-Hematologic DLT

Any Grade 3 or greater non-hepatic non-hematologic toxicity will be considered as a DLT with the following specific **exceptions**:

- Grade 3 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention.
- Grade 3 nausea or vomiting that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention.
- Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis.

- Isolated Grade 3 fever that lasts ≤3 days and is not associated with hemodynamic compromise (i.e., hypotension, clinical or laboratory evidence of impaired end-organ perfusion).

Dose-limiting immune-related AEs will be defined as follows:

- Any Grade 2 or greater eye pain or reduction in visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy or any Grade 2 or greater eye pain or reduction in visual acuity that requires systemic treatment.
- Any other Grade 3 or greater irAE.

Infusion Reaction and DLT

Grade 3 or Grade 4 infusion reactions will also be considered as DLTs.

C. Hematologic DLT

Hematologic DLT will be defined as follows:

- Grade 4 neutropenia ≥7 days in duration
- Grade 4 thrombocytopenia, or any Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade ≥3 febrile neutropenia
- Grade ≥3 hemolysis.

In order to be evaluable for DLT, subjects must 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. Subjects who experience DLT within the first 2 weeks after having received 100% of assigned dose of HBI-8000 are also evaluable for DLT. Full dose of nivolumab will be administered according to Opdivo® Prescribing Information (Appendix 9).

Laboratory measurements and other tests appropriate to the clinical situation may be performed more frequently than stipulated in the Schedule of Events, in order to determine DLTs.

3.3 Dose Reduction and Interruption

3.3.1 HBI-8000 Dose Reduction

If a subject experiences any of the toxicities described in Section 3.2.4, the dose of HBI-8000 will be reduced to one dose level lower (see Section 3.2.1, Table 1). Treatment will resume only after toxicity has returned to Grade ≤1 within 14 days from the occurrence of the toxicity. For neutropenia, the use of granulocyte-colony stimulating factor (G-CSF) should be considered to shorten resolution time. If the same toxicity recurs despite dose reduction, HBI-8000 will be discontinued. One dose reduction for non-hematological toxicities and two dose reductions for hematological toxicities are allowed. Should toxicity be deemed not related to nivolumab, a subject may continue to receive nivolumab at the discretion of Investigators. Once the dose of HBI-8000 is reduced, it will not be increased. This dose reduction guideline applies to the entire study duration.

3.3.2 HBI-8000 Dose Delay Independent of Nivolumab Administration

At the discretion of the Investigator, the dose may also be delayed for up to 14 days from the scheduled time of dosing, for any toxicity possibly or probably related to HBI-8000 that does not meet toxicity criteria described in Section 3.2.4. More specifically, in the event of uncomplicated thrombocytopenia Grade 3 or neutropenia Grade 3, dosing of HBI-8000 should be held until recover to Grade ≤1 before resume. Supportive care with hematological growth factors may be applied at the discretion of Investigator.

In case of Grade 2 prolongation of QTc interval (481 to 500 ms) the subject should be closely monitored and in case of Grade 3 QTc prolongation (≥501 ms) (CTCAE v4.03) dosing should be delayed until it is resolved to Grade ≤1 within 2 weeks. If recovery takes more than 2 weeks study drug should be discontinued.

Dosing may be interrupted to assess or treat intercurrent illnesses. The Sponsor should be notified of any treatment interruption. An interruption of >14 days will require the subject to be removed from the study treatment (except in case of potential subject benefit, which must be approved by the Sponsor).

Should treatment with HBI-8000 be discontinued, the subject may continue to receive nivolumab under standard of care at the discretion of the Investigator. The subject will have an End-of-Treatment safety visit 30 days after the last dose of HBI-8000 and will not be followed for new adverse events thereafter. Tumor assessments will continue until disease progression or initiation of new anti-cancer treatment for a maximum of 12 months after the last dose of HBI-8000.

3.3.3 Nivolumab Dose Delay Independent of HBI-8000 Administration

Investigators should withhold a dose as described in Table 4 (based on Opdivo® Prescribing Information Recommended Dose Modifications), until it is resolved to Grade 1 or lower. Once resolved, the dose can be reinstated. For subjects who were treated with steroids for irAE, steroids need to be tapered over at least 1 month before resuming nivolumab. The administration of HBI-8000 will continue as scheduled during nivolumab dosing interruption.

3.3.4 Duration of HBI-8000 Administration

HBI-8000 may be administered up to 24 months or until one of the following criteria applies:

- Disease progression confirmed by imaging studies according to iRECIST
- Unacceptable AE(s)
- Toxicities requiring HBI-8000 dosing delay >14 days more than twice, or recurring unacceptable toxicity despite one dose reduction and optimal supportive care
- Consent withdrawal to study treatment or the entire study participation
- Judgment of the Investigator
- Death

For subjects receiving clinical benefit at the end of 24 months, further treatment with HBI-8000 will be discussed between Sponsor and Investigator on a case-by-case basis. These subjects may be entered to the treatment Extension Phase after the end of the main study.

3.4 Duration of Follow-Up

All subjects with ongoing treatment related toxicity at the end of a treatment visit will be followed for at least one month, until resolution to Grade ≤1, or stabilization of the toxicities, whichever is last.

For subjects receiving RP2D in the dose escalation phase and those enrolled in the Phase 2 portion of the study, if disease progression has not been observed at the end of HBI-8000 administration, their tumor status will be followed to obtain the date of progression, initiation of another anti-cancer treatment, or referral to hospice.

3.5 Duration of Study

Approximately 6 to 12 months are allocated to enroll subjects in Phase 1b, and 24 to 36 months in the Phase 2 portion of this study for each patient population. Subjects may be treated in this study as long as they receive clinical benefit (SD or a response) in the absence of unacceptable toxicity up to 24 months. For subjects who continue to receive clinical benefit at the end of 24 months, further treatment with HBI-8000 will be discussed between Sponsor and Investigator on a case-by-case basis and may be entered into the treatment Extension Phase. Duration of follow-up will be as described in Section 4.3.4.

3.6 End of Study

This study consists of a dose escalation portion (Phase 1b) and a tumor-specific cohort expansion portion (Phase 2). The primary analysis for Phase 1b will focus on safety. It is planned after the last subject has been observed for at least 4 months from the initiation of study treatment.

Phase 2 of this study plans to explore the efficacy in selected tumor indications. Analysis of efficacy data will be performed separately according to tumor type studied. For a given indication, preliminary efficacy will be analyzed when tumor response from the last subject becomes available. The efficacy data cut-off for the main study will occur when the last subject receiving HBI-8000 has been monitored for tumor response for at least 12 months or all subjects have shown disease progression, whichever is earlier. Data obtained up to the main cut-off date will be analyzed for overall efficacy.

Safety data cut-off for the main study will occur after efficacy data cut-off and include End of Treatment safety visit and applicable safety follow-up based on assessment at EoT. Subjects with clinical benefit at the time of the main data cut-off will be entered in the Extension Phase of the study to continue HBI-8000 treatment and be monitored for safety until meeting criterion necessitating treatment discontinuation as described in Section 3.3.4. In the Extension Phase, safety data and dosing information will be collected same as in main study, however, collection of tumor response will be based only on reports by investigator as PD, SD, PR, and CR at intervals according to standard of care. Once all subjects in Extension Phase discontinue receiving HBI-8000 and complete EoT assessment (Section 4.3.4) safety data from the Extension Phase will be integrated with the safety data of the main study and analyzed for overall safety of

the study. The final analysis of safety for the entire study is planned at 3 months after the last subject discontinues study treatment.

4 STUDY PROCEDURES

4.1 Study Population

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). Under no circumstances will subjects who enroll in this study and have completed treatment as specified, be permitted to enroll for a second time.

4.1.1 Inclusion Criteria

Subjects with advanced malignancies being treated with nivolumab, an FDA-approved medication, may be entered in the study only if they meet **all** of the following criteria:

1. Adults at least 18 years of age.
2. ECOG performance status ≤1.
3.
    a. Subjects with histopathologically or cytologically confirmed diagnosis of non-uveal melanoma, RCC, or NSCLC, for whom the use of nivolumab is indicated. NSCLC subjects with EGFR or ALK genomic aberrations in tumor should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab **(Phase 1b).**
    b. Subjects with histopathologically or cytologically confirmed diagnosis of non-uveal melanoma or NSCLC, for whom the use of nivolumab is indicated **(Phase 2 expansion)**. With Protocol Amendment 5, subjects with NSCLC are not eligible for enrollment.
    c. Non-uveal melanoma and NSCLC patients whose disease has progressed after achieving SD for at least 3 months, PR or CR as the best response that has been documented by imaging studies on previous treatment with a PD-L1 inhibitor with proven efficacy **(Phase 2 expansion).** With Protocol Amendment 5, subjects with NSCLC are not eligible for enrollment.
    d. 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).
4. Subject must have at least one measurable target lesion as defined by RECIST v1.1. Melanoma subjects participating in optional correlative sub-study must have tumor tissue available for biopsy from a metastatic or unresectable site for PD-L1 and correlative biomarker analysis.
5. All prior systemic therapy (chemotherapy, mutation targeting therapy, immune checkpoint therapy), surgical or radiation treatment must have been completed at least 4 weeks before study drug administration (2 weeks for palliative radiotherapy, 1 week for minor surgery) pending full recovery from therapy.
6. The following laboratory results within 7 days prior to study drug administration: Adequate hematopoietic, electrolyte, hepatic, and renal laboratory findings as defined below: white blood cells (WBC) ≥3000/μL, neutrophils ≥1500/μL, platelets ≥100 x 10^3/μL, hemoglobin ≥9.0 g/dL independent of transfusion, creatinine ≤1.5 mg/dL,

AST and ALT ≤3 x ULN, alkaline phosphatase ≤2.5 x ULN unless bone metastases present, bilirubin ≤1.5 x ULN (unless known Gilbert's disease where it must be ≤3 x ULN), and serum albumin ≥3 mg/dL.

7. Life expectancy ≥12 weeks.
8. A negative serum pregnancy test at baseline for women of childbearing potential.
9. Are willing to abstain from heterosexual activity or practice physical barrier contraception prior to time of study entry to at least 5 months after the last day of treatment.
10. Have the ability to understand and the willingness to sign a written informed consent document.

4.1.2 Exclusion Criteria

Subjects who meet **any** of the following criteria at screening will **not** be eligible for the study:

1. History of Grade 3 or above hypersensitivity reactions to other monoclonal antibodies.
2. Subjects with a history of a cardiovascular illness including: congestive heart failure (New York Heart Association Grade III or IV); unstable angina or myocardial infarction within the previous 6 months; or symptomatic cardiac arrhythmia despite medical management. In addition, for Phase 1b only: QTcF >450 ms in male, and >470 ms in female, congenital long QT syndrome.
3. Uncontrolled hypertension, systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg.
4. Subjects with active brain metastasis; previously treated brain metastasis is allowed if it has been stable for 4 weeks or more and not requiring steroids.
5. Presence of leptomeningeal disease.
6. History of hemorrhagic diarrhea, inflammatory bowel disease, active uncontrolled peptic ulcer disease, or recurrent pleural effusion requiring repetitive palliative thoracentesis within 3 months prior to study entry except for subjects with a pleurex port; and immune-mediated toxicity leading to treatment discontinuation.
7. Active, known, or suspected serious autoimmune disease, except for type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia).
8. Active uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
9. Known history of testing positive for human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS).
10. Active hepatitis B (serum hepatitis B surface antigen [HBV sAg] positive), or hepatitis C (hepatitis c virus [HCV] antibody test or serum hepatitis C ribonucleic acid [RNA] positive) indicating acute or chronic infection.

11. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted.
12. Use of other investigational agent (drug not marketed for any indication) within 28 days or at least 5 half-lives (whichever is shorter) before study drug administration.
13. Pregnant or breast-feeding women.
14. Second malignancy unless in remission for 2 years except for non-melanomatous skin cancer, carcinoma *in situ* of the cervix treated with curative intent, curatively treated prostate cancer with prostate specific antigen (PSA) <0.1 ng/mL.
15. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events.
16. Unwilling or unable to comply with procedures required in this protocol.

4.2 Subject Registration and Dose Level Assignment

Based on medical history, potentially eligible subjects will be identified. After obtaining informed consent, the screening procedures will be performed. Once a subject's eligibility has been confirmed, a 6-digit subject number will be assigned. The first 2 digits are the site number (provided by the Sponsor to investigational sites). The following 2 digits are the cohort number (for dose levels in Phase 1b; or tumor indication in Phase 2), and the last 2 digits are a sequential number within an investigational site. During the Phase 1b dose escalation phase, dose levels will be assigned to subjects registered sequentially across study sites.

If a subject is registered to the study and later found unable to begin HBI-8000 administration, the subject will be replaced.

4.2.1 Blinding

This is an open-label study; no randomization or blinding procedures will be performed.

4.3 Study Procedures Overview

Subjects will be screened by the study center Investigator or study nurse prior to entry into the study. Subjects will receive a detailed explanation of the study design, and the potential risk/benefit of treatment will be disclosed to subjects prior to the screening process. Only eligible and consenting subjects will be entered into the study. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure.

The Schedule of Dosing and Assessments is presented in Appendix 1.

4.3.1 Screening Assessments (within 28 Days prior to Start of Treatment)

Screening assessments include informed consent, medical history, documentation of melanoma (including BRAF mutation status for the Phase 2 portion), RCC or NSCLC diagnosis (including EGFR and ALK mutation status if available), tumor PD-L1 expression (historical data when

available), treatment history, baseline conditions, demographics, height, anti-HBV and anti-HCV tests, concomitant medications, brain magnetic resonance imaging (MRI), if clinically indicated, and radiographic tumor assessment. If a subject has metal implants, a computed tomography (CT) scan should be used instead of an MRI.

4.3.2 Baseline Assessments (within 7 Days of Start of Treatment)

Baseline assessments include physical examination, vital signs, ECOG performance status, weight, concomitant medications, laboratory tests (hematology, chemistry, coagulation and urinalysis), serum pregnancy test (if applicable), and safety ECG. Phase 2 includes tumor tissue biopsy in melanoma subjects (if participating in optional serial tumor biopsy sub-study) and PBMC and plasma collection. The baseline PBMC and plasma samples must be collected prior to any treatment and may occur at Cycle 1 Day 1 pre-dose.

4.3.3 Treatment Phase

Physical and laboratory assessments will be performed according to the Schedule of Dosing and Assessments (see Appendix 1). For C1D1 and Cycle 1 Day 15 (C1D15), a 24-hour window is allowed to accommodate PK studies, Holter ECG, safety labs and physical examination. All visits and assessments after C1D15 onwards may be performed ±3 days to accommodate unforeseen delays, holidays, or vacations. First assessment of tumor response will be scheduled in the last week of Cycle 2 and every 8 weeks (±3 days) thereafter, or sooner if a subject develops clinical signs and symptoms of disease progression, until PD or end of study treatment.

In the Extension Phase of the study, tumor status (PD, SD, PR, or CR) will be followed by phone calls or e-mail at intervals according to standard of care until subject discontinues the study. Safety will be monitored as described for the main study.

4.3.4 Subject End-of-Treatment (EoT) Safety Follow-up Visit

The safety follow-up visit will be conducted 30 (±3) days following the last dose of HBI-8000 or before the initiation of new cancer treatment, whichever is earlier. Assessments will include physical examination, vital signs, body weight, concomitant medications, ECOG performance status, hematology, blood chemistry, urinalysis, pregnancy test (if applicable), ECG, and assessment of any ongoing adverse events.

Any pregnancies while on this study or within 30 days of the last dose of the study drug will be followed up, with subject permission, until the birth of the baby.

4.3.5 Tumor Status and Adverse Events Follow-up

For the main study, follow-up for tumor status in subjects in whom disease progression has not yet been observed should occur at 12 (±1) week intervals after the last dose of HBI-8000 until progression, initiation of new anti-cancer treatment, or referral to hospice (unless consent is withdrawn), for up to 12 months after the last dose of HBI-8000 or the end of the main study. Subjects with study treatment related adverse events of Grade ≥2 at EoT visit should be assessed monthly (phone calls/clinic visits) until the adverse events have resolved to Grade ≤1 or are determined to be chronic, or subject receives other anti-cancer therapy.

In the Extension Phase, tumor status will be followed by phone calls or e-mail intervals according to standard of care until subject discontinue the study. Safety will be monitored as described for the main study.

5 STUDY TREATMENTS

5.1 Treatments to be Administered

A treatment cycle is defined to be 28 days for the conduct of study. Study drug administration will continue until disease progression or unacceptable toxicity.

HBI-8000 administration will begin on Day 1 and continue every 3 to 4 days on the twice weekly schedule without interruption (e.g., Monday/Thursday, Tuesday/Friday). Subjects are required to take HBI-8000 tablets approximately 30 minutes after a meal, not before the meal. For Phase 1b, after taking their oral dose of HBI-8000, subjects will receive nivolumab 240 mg by IV infusion over a period of 60 minutes as recommended in the OPDIVO® Prescribing Information (Package Insert). For Phase 2, after taking their oral dose of HBI-8000, subjects will receive nivolumab by IV infusion over a period of 60 minutes as recommended in the OPDIVO® Dose and Prescribing Information (Package Insert) and in accordance with Appendix 9.

To manage infusion reactions, study drug will only be administered at the sites that are fully equipped, and study personnel are properly trained.

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 Schedule of Dosing and Assessments (see Appendix 1) and Appendix 2 and Appendix 3. For PK sampling, plasma will be collected in dipotassium ethylenediamine tetraacetic acid (K_2EDTA) tubes for analysis of HBI-8000 concentrations. For sites and subjects participating in biomarker correlative studies, samples will be collected as described in Appendix 8. In the Phase 1b portion of the trial only, to accommodate the QTc study of HBI-8000 in Cycle 1 Day 1, subjects will receive nivolumab 240 mg by IV infusion over 60 minutes on Days 2 and 15 of Cycle 1. For Cycle 2 and beyond, nivolumab will be administered on Days 1 and 15 of the Cycle.

Administration of HBI-8000 will be continued until there is radiographic evidence of progressive disease according to iRECIST, unacceptable treatment-related adverse events, the subject withdraws from study treatment, or at the request from the Investigator based on clinical judgment. For subjects discontinued from HBI-8000 treatment in the absence of disease progression, the subjects may continue to receive nivolumab under standard of care per Investigator's discretion and be followed for disease response as long as consent to study participation remains effective. Similarly, nivolumab administration may be discontinued due to unacceptable toxicities associated with nivolumab or based on Investigator's clinical judgement. In this case, the subject may continue to receive HBI-8000 and be followed for study response as long as consent to study participation remains effective.

5.2 Identity of Investigational Products

Both HBI-8000 and nivolumab, are manufactured in the US.

Table 2: Investigational Products

Investigational Product	Dosage Form and Strength	Manufacturer
HBI-8000, chidamide	Immediate-release 10 mg film coated tablets	[redacted]
OPDIVO®, nivolumab	40 mg/4 mL single-use vial (0003-3772-11) and 100 mg/10 mL single-use vial (0003-3774-12)	[redacted]

With Protocol Amendment v8.0, remaining subjects in the Extension Phase of the study will receive the HBI-8000 treatment as film coated tablets.

HBI-8000: The HBI-8000 Drug Product is formulated as a film coated tablet containing [redacted]

The drug substance, drug product intermediate (dispersion), and film coated tablets are manufactured in the US.

Nivolumab is an IgG4 kappa immunoglobulin supplied as a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. [redacted]

The vial should be visually inspected for particulate matter and discoloration prior to administration. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

5.3 Packaging and Labeling

HBI-8000 tablets are packaged in HDPE bottles closed with an induction seal and a child-resistant cap. Each bottle contains twenty-six (26) 10 mg tablets, a desiccant pack, and a cotton coil.

Nivolumab is supplied in single-use vials [OPDIVO®(nivolumab) USPI, 2020]. Commercial nivolumab will be obtained directly by the site for use during this study and charged to the subject and/or third-party payer, as usual. If a prospective subject cannot afford the cost of nivolumab or the copays, the study site will work with the study team on possible provisioning of nivolumab through a central sourcing solution or reimbursement, as appropriate.

5.4 Investigational Products Storage

HBI-8000: Storage and distribution of HBI-8000 should be at 15°C to 30°Celsius (°C) (59°F to 86°Fahrenheit [°F]). HBI-8000 must be stored out of the reach of children and in the original container with tightly closed cap to protect from moisture.

Nivolumab: Should be stored under refrigeration at 2°C to 8°C (36°F to 46°F), protected from light by storing it in the original package until time of use. It should not be frozen or shaken.

5.5 Prior and Concomitant Treatments

All concomitant medications received by the study subjects must be recorded on the electronic case report form (eCRF).

5.5.1 Excluded Medications and Therapy

Concomitant administration of the following types of drugs is not allowed:

- Recently completed drug-drug interaction study showed an approximate 40% increase in AUC of HBI-8000 when itraconazole, a strong CYP3A4, was administered concurrently. The use of potent CYP3A4 inducers or inhibitors (see Appendix 6) should be avoided. The washout period for these agents prior to study initiation is 7 days.
- During the Phase 1b portion of the study, drugs known to cause QT/QTc prolongation should be discontinued at least 14 days prior to the 1st dose of HBI-8000 (Cycle 1 Day 1) when QT/QTc study will be performed, and substituted with alternative therapy, as needed. For example, when a serotonin-3 antagonist is required, palonosetron (Aloxi®) should be prescribed instead of ondansetron (Zofran®). After QT/QTc study, they are allowed but should be avoided if alternative therapy is available. (Phase 1b only).
- Concomitant administration of anti-tumor treatment other than the study drug, or procedure that could interfere with the evaluation of safety or anti-tumor effect of study drug is prohibited during the study.
- Any live / attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

5.5.2 Allowable Medications

Systemic use of corticosteroids at doses ≤10 mg/day of prednisolone or converted equivalent dose, is permitted during the study. Brief use of higher dose of prednisone or its equivalent is also permitted to manage immune related toxicities as indicated. Supportive care to mitigate toxicities such as anti-emetics for nausea, and G-CSF for neutropenia are also allowed.

Subjects should consult their Investigator prior to using medications other than the study drug, including over-the-counter medications and supplements.

5.5.2.1 Supportive Care and Prohibited Medications

In order to provide optimal subject care and to account for individual medical conditions, the Investigator may apply discretion to prescribe supportive care (e.g., acetaminophen, diphenhydramine, antimicrobials) according to local institutional guidelines.

Subjects must be instructed not to take any additional medications (including over-the-counter products) during the study without prior consultation with their study doctor.

5.6 Dietary Restrictions

Due to potential food-drug interactions, grapefruit, grapefruit juice, Seville oranges, and any products that contain Seville oranges or grapefruit should be avoided within 7 days prior to Day 1 Cycle 1 in the Phase 1b portion, and the Phase 2 portion of the study through 7 days after the last dose of HBI-8000.

On dosing days, HBI-8000 should be taken in the morning, approximately 30 minutes after breakfast. On the days when PK and QTc studies are performed, the time of administration may be adjusted to meet the clinical schedule.

5.7 Subject Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

The subject will be provided with a drug log to record times of administration, side effects, and missed doses. The subject will be instructed to bring the drug log and study drug bottles (including any empty bottles) in the provided cooler with refrigerated gel pack to each appointment for reconciliation.

At each visit, prior to dispensing study medication, previously dispensed study medication will be confirmed by the Investigator and compliance assessed. Subjects exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking less than 75% of study medications during a treatment cycle.

5.8 Study Medication Accountability

A clinical supply shipment and receipt verification form will be enclosed with each study drug shipment. The site study pharmacist who receives the shipment should complete this form and return a signed copy to the Sponsor or its representative.

The Investigator, or his/her designee, must maintain a complete and accurate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms will be described in detail in the pharmacy manual and must be available for inspection at any time.

All study medication must be accounted for at the termination of the study, and a written explanation provided for any discrepancies. All unused study medication and packaging materials are to be inventoried and returned or destroyed as per the site's Standard Operating Procedure (SOP) on Drug Disposition. The Investigator is not permitted to destroy unused clinical drug supplies or packaging materials unless authorized by the Sponsor or its representative.

6 STUDY ASSESSMENTS

6.1 Efficacy Assessments

All measurable disease (target lesions and non-target lesions) must be documented at screening and re-assessed at each subsequent tumor evaluation. Re-assessment will be done by imaging studies according to RECIST Guidelines v1.1, and iRECIST, along with physical examinations and other methods as needed. At the Investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected. For a CT scan, it is recommended, for purposes of consistency and radiation protection, to reconstruct 5-mm slices (or less) contiguously. A measurable lesion should be at least twice the slice thickness at baseline, i.e., 10 mm if slice thickness is 5 mm. This is also applicable for MRI examinations.

Tumor response will be evaluated by the Investigator using the RECIST v1.1 criteria [Eisenhauer et al., 2009] and iRECIST [Seymour et al., 2017]. Taking into consideration possible pseudo-progression, the subject may continue study treatment until the next imaging evaluation to assess tumor response. The same scanning modality should be used at baseline and throughout treatment for each subject.

6.2 Safety Assessments

Treatment-emergent adverse events reported by the subjects or observed during physical examination will be assessed according to NCI-CTCAE v 4.03 (CTCAE home page: http://evs.nci.nih.gov/ftp1/CTCAE/About.html) and recorded by severity grades and association with study treatment. Results of clinical laboratory tests, vital signs, physical findings, ECGs and ECOG performance status will be monitored and recorded.

6.2.1 Vital Signs, ECG, Physical Examinations, and ECOG Assessments

Vital sign measurements will include heart rate, SBP, and DBP in a supine position. Vital sign measurements should be performed prior to the ECG and after the subject has been supine for at least 5 minutes.

Physical examinations will include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

ECOG performance status will be assessed as follows (see Appendix 4 for Karnofsky and ECOG scores conversion table) [Oken et al., 1982]:

Table 3: ECOG Performance Status

Grade 0	Fully active, able to carry on all pre-disease performance without restriction
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Grade 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Grade 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Grade 5	Dead

6.2.2 Clinical Laboratory Assessments

Hematology testing will include the following parameters: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

Coagulation will include the following parameters: prothrombin time (PT), activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR).

Serum chemistry testing will include the following parameters: 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), total triiodothyronine (total T3), free thyroxine (free T4) (direct), total protein, albumin, uric acid, alkaline phosphatase, sodium, potassium, calcium, magnesium, phosphorus and glucose.

Urinalysis will be performed using a dipstick method followed by microscopic examination in the event of abnormal dipstick results.

Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at baseline and at the EoT safety visit. Women of childbearing potential are defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal, defined as ≥12 months of amenorrhea.

6.3 Pharmacokinetic Assessments

In Part 1, the dose escalation phase, and Part 2, the cohort expansion phase, subjects will have plasma sampled according to the respective sparse sampling schema (see Appendix 2and Appendix 3) for the POPK analysis.

In conjunction with the POPK analysis, in Phase 1b, ECGs in triplicate will be obtained to investigate the effect of HBI-8000, if any, on QTc intervals (see Section 6.4.2). The schedule for ECG/QTc assessment is described in Appendix 2. Only ECGs obtained for the QTc study will be reviewed at a central laboratory.

Samples of whole blood will be obtained in a Vacutainer® tube containing K_2EDTA anticoagulant for the determination of HBI-8000 and its metabolites in human plasma prior to HBI-8000 administration and at subsequent time points (see Appendix 2 and Appendix 3). Details regarding sample collection, processing and transport will be included in the study

manual. The following information will be captured for blood sample collection in each subject's eCRF:

1. Subject's number and initials.
2. Time and date of dose administration.
3. Time and date of each blood sample collected for PK analysis.
4. Time and date of subject's most recent ingestion of food prior to dose administration.

6.4 Pharmacodynamics Assessments

6.4.1 PBMC Histone Acetylation (Phase 2)

In the Phase 2 portion of the study, blood samples for histone acetylation analysis will be collected at time points shown in Appendix 1. PBMC will be processed, frozen and banked for analysis. See Appendix 5 for sample handling procedures.

6.4.2 Holter ECG (QTc) Assessments (Phase 1b)

In Phase 1b, 12-lead Holter monitoring will be performed as detailed in Appendix 2. Only ECGs obtained for the QTc study will be reviewed at a central laboratory.

An IQVIA ECG central laboratory will provide digital 12-lead Holter monitors to all clinical sites. On each Holter recording day, a continuous Holter will be recorded over a time period starting 1 hour before breakfast until 4 hours post-dose. Assuming HBI-8000 will be administered approximately 30 minutes after completing breakfast, the total monitored duration will be approximately 6 hours. From these continuous Holter recordings, 10-second ECGs will be extracted at the specific time points listed in Appendix 2.

The same recorder will be used for all recordings for a subject. Date and time settings must be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparation must be thorough and electrode positions must be according to electrode positions recommended by the central laboratory manual. Electrode positions will be marked with an indelible pen at the start of the study day to ensure exact reposition. Electrodes will be applied 1.5 hours before breakfast and left in place for the duration of the recording on each relevant study day.

The 12-lead continuous digital ECGs will be recorded and transmitted to the IQVIA ECG central laboratory, according to IQVIA standard procedures for settings, recording, and transmission of digital ECGs.

Prior to each time point at where an ECG is to be extracted from the continuous Holter recording, subjects must rest in a supine position for approximately 15 minutes.

The 5-minute extraction window will be provided to the ECG central laboratory for each of the specified time points. The central laboratory will perform the ECG extractions within this given window. If the quality seems to be poor within this window, then the remainder of the supine window can be utilized for the extractions.

On days when digital ECG Holter measurements are being taken, subjects should be restricted to a low level of physical activity and should refrain from any activities likely to stimulate or excite them (e.g., video games, stimulating movies or television shows). Additionally, they should refrain from using hand-held electronic or electrical devices (e.g., cell phones, hair dryers) as these have a potential to interfere with ECG signals. Food and drink should be restricted to the times specified in the protocol as this also has the potential to affect ECG signals. Date and time of intake (start and completion) of any food during the Holter recording period will be recorded on the eCRF.

Triplicate 10-second ECGs will be extracted from the Holter flashcard at each of the specified time points by the Holter team at the IQVIA ECG central laboratory. Each ECG replicate will be analyzed by the cardiologist who will be blinded to subject identifiers, time, and treatment. ECGs will be analyzed for PR, QRS, RR, and QT intervals and morphological changes by experienced cardiologists. A limited number of skilled readers will be employed in the over-read process to control for variability in interpretation. All ECGs from a single subject will be read together by the same reader, blinded to visit and time.

ECG interval data will then be transmitted to the IQVIA statistician for further analysis, as described in Section 7.15.2.

6.4.3 Immune Correlative Sub-study

To characterize patient immune response during treatment with HBI-8000 and nivolumab, PBMC and plasma will be collected at baseline and various time points throughout treatment (Appendix 8). PBMCs will be processed for fluorescence activated cell sorting (FACS) to characterize T-cell subtypes and other immunocytes, e.g., MDSC, NK, B cells, and intracellular cytokine levels (e.g., interferon-gamma, IL-6 and IL-10). Corresponding plasma will be banked frozen and analyzed by multiplex for cytokines, chemokines, and other soluble factors.

In subjects who have consented to optional serial tumor tissue biopsies, core needle or fine needle biopsies will be analyzed by RNA sequencing and nanostring technology to determine immune activation status in tumor microenvironment over the course of study treatment. In selected cases, histopathology examination will be carried out to corroborate with findings made from RNA sequencing and nanostring technology.

6.5 Timing of Study Assessments

6.5.1 Screening Assessments (within 28 Days prior to Start of Treatment)

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for all subjects screened (whether enrolled or not) will be maintained at the study site.

All screening and baseline assessments must be completed and reviewed to confirm that subjects meet all eligibility criteria. An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed, submitted for review/approval by the Sponsor or its designee and kept at the investigational site.

Screening assessments include informed consent, medical history, documentation of melanoma (including BRAF mutation status for the Phase 2 portion), RCC or NSCLC diagnosis (including EGFR and ALK mutation status if available), tumor PD-L1 expression (historical data when available), treatment history, baseline conditions, demographics, height, anti-HBV and anti-HCV tests, concomitant medications, brain MRI, if clinically indicated, and radiographic tumor assessment (Appendix 1). If a subject has metal implants, a CT scan should be used instead of an MRI.

Screening assessments will be performed within 28 days prior to Day 1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used (and do not need to be repeated during screening unless they do not meet the criteria defined in the protocol).

6.5.2 Baseline Assessments (within 7 Days of Start of Treatment)

Baseline assessments include physical examination, vital signs, ECOG performance status, weight, concomitant medications, laboratory tests (hematology, chemistry, coagulation and urinalysis), serum pregnancy test (if applicable), and safety ECG. Phase 2 includes tumor tissue biopsy in melanoma subjects (if participating in optional serial tumor biopsy sub-study) and PBMC and plasma collection. The baseline PBMC and plasma samples must be collected prior to any treatment and may occur at Cycle 1 Day 1 pre-dose.

For melanoma subjects participating in the optional serial tumor biopsy sub-studies in Phase 2, tumor tissue biopsy will be obtained. If a subject had tumor specimen obtained after completing previous therapy and before entering into current study, HUYABIO should be consulted to determine if the historical specimen is acceptable as the protocol pre-treatment specimen in the optional serial tumor biopsy sub-studies.

6.5.3 Assessments during Study Treatment

All assessments must be performed as per Schedule of Dosing and Assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

For C1D1 and C1D15, a 24-hour window is allowed to accommodate PK studies, Holter ECG, safety labs, and physical examination. All visits and assessments after C1D15 onwards may be performed ±3 days to accommodate unforeseen delays, holidays, or vacations.

Assessment of tumor response will be scheduled in the last week of Cycle 2 including C3D1 and then every 8 weeks (± 3 days) thereafter, or sooner if subjects develop clinical signs and symptoms of disease progression, until PD or end of study drug treatment. If a subject discontinues study drug before PD is recorded, tumor assessments are to be performed every 12 (±1) weeks until PD, initiation of another anti-cancer treatment, or referral to hospice (unless consent is withdrawn) for up to 12 months after the last dose of HBI-8000 or the end of the main study.

Target lesion and non-target lesions will be assessed by CT and/or MRI scanning, with response and progression evaluated by RECIST v1.1 criteria.

Blood samples for PBMC histone acetylation analysis will be collected at baseline, and then on Day 1 of Cycles 2, 3, and 4 before study treatment administration.

6.5.4 End-of-Treatment (HBI-8000) Safety Follow-up Visit

All subjects receiving at least one dose of HBI-8000 and discontinuing treatment for any reason except death or withdrawal of consent, will be assessed 30 (±3) days after the last dose of study treatment or before the initiation of new cancer treatment, whichever is earlier. Assessments will include: physical examination, vital signs, body weight, concomitant medications, ECOG performance status, hematology, blood chemistry, urinalysis, pregnancy test (if applicable), and ECG.

Subjects with HBI-8000-related AEs of Grade ≥2 observed at the EoT visit should be followed up and assessed monthly (phone calls/clinic visits) until the AEs have resolved to Grade ≤1 or are determined to be chronic, or subject receives other anti-cancer therapy.

Any pregnancies while on this study or within 30 days of the last dose of the study drug will be followed up, with subject's permission, until the birth of the baby.

Subjects entering the Extension Phase for continued HBI-8000 treatment will have their EoT visit deferred until they discontinue their Extension Phase treatment. The EoT safety assessments will be conducted 30 (±3) days after the last dose of Extension Phase treatment.

6.5.5 Tumor Status Follow-up

Follow-up for tumor status in subjects in whom disease progression has not yet been observed should occur at approximately 12 (±1) week intervals after the last dose of HBI-8000. The follow-up to tumor status ends when disease progression occurs, new anti-cancer therapy begins, or referral to hospice for a maximum of 12 months after the last dose of HBI-8000 or the end of the main study. The first subsequent anti-cancer therapy should be recorded with regimen and start date in the appropriate eCRF.

6.5.6 Subject Withdrawal

Subjects have the right to withdraw from the study at any time for any reason, and the Investigator should try to ascertain the reason for withdrawal as completely as possible. The Investigator also has the right to decide whether a subject should be discontinued from the study. Study treatment with HBI-8000 may be discontinued and the subject withdrawn from the study under the following circumstances:

- Unacceptable toxicity (adverse event)
- Progression of the disease under study
- Decision by the Investigator or subject to permanently discontinue study drug administration
- Intercurrent illness that would, in the judgment of the Investigator, affect clinical assessments, subject safety, or follow-up to a significant degree
- Significant protocol deviations that jeopardize the usefulness of the data
- Subject noncompliance

- Subject is beginning another anti-cancer treatment protocol
- Subject becomes pregnant
- Subject request to withdraw informed consent
- Death

All subjects who withdraw from study treatment must complete an end-of-study safety follow-up visit, to be performed 30 (± 3) days after the last study treatment (see Appendix 1). Any subject who has not withdrawn consent should be followed for disease progression if not already recorded.

It is important to distinguish between discontinuation from treatment and discontinuation from the study. A subject may withdraw consent for treatment but still allow follow-up, in which case he/she should be followed for safety and disease status. If a subject has withdrawn consent for any follow-up, he/she may not be followed for any reason.

Subjects who are lost to follow up or withdraw consent for study participation prior to receiving HBI-8000 or who withdraw in Cycle 1 for reasons unrelated to drug toxicity may be replaced.

6.6 SAFETY

6.6.1 Definitions

6.6.1.1 Adverse Events

An AE is any unfavorable and unintended sign (including any clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Assessment of the occurrence of an AE will be based on changes in the subject's physical examination, laboratory results, and/or signs and symptoms. An AE also includes any newly occurring event or previous condition that has increased in severity or frequency after the subject received the first dose of study medication.

Adverse events will be monitored until they are resolved or clearly determined to be due to a stable/chronic condition or intercurrent illness. Medical care will be provided, as defined in the informed consent, for any AE related to study participation.

6.6.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence, regardless of its relationship to study drug, that at any dose:

- Results in death.
- Is life-threatening (i.e., the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires in subject hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical or surgical) to prevent one of the other serious outcomes listed in the definition of an SAE. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Although overdose is not always serious by regulatory definition, this event should be reported on an AE/SAE form and sent to the Sponsor in an expedited manner. Overdose is defined as administration to the subject of a dose of test article that exceeds by more than 50 mg/dose or 100 mg/week for HBI-8000, and any dose above the approved 240 mg every 2 weeks or 480 mg every 4 weeks for nivolumab. Any overdose of study drugs should be reported via an AE/SAE form within 24 hours of Investigator awareness of the overdose to the Sponsor, regardless of association with an AE. In the case that the overdose did not result in an AE, the Investigator should report this as "overdose, no AE" on the AE/SAE form and specify the intended amount, as well as the actual amount, of drug administered.

All pregnancies, regardless of outcome, must be reported to the Sponsor on a pregnancy surveillance form, and not an AE/SAE form.

NOTE:

The following hospitalizations are not considered SAEs in sponsored clinical studies:

- A <24-hour visit to the emergency room or other hospital department, that does not result in admission (unless considered to be an important medical event or an event that is life threatening)
- Elective surgery planned prior to signing ICF
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for pretreatment assessment/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for a purpose other than remedying ill state of health and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission for a life circumstance that has no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative)
- Admission for progressive disease

6.6.2 Intensity of Adverse Events

The intensity of adverse events will be graded according to the NCI-CTCAE scale:

- **Grade 1: Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2: Moderate**; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Grade 3: Severe or medically significant**, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.
- **Grade 4: Life-threatening** consequences; urgent intervention indicated.
- **Grade 5: Death** (at least possibly) related to the AE.

6.6.3 Assessment of Causal Relationship to Study Drug

The relationship of an AE to the study medication is to be graded by the Investigator as follows:

Definite:

- Distinct temporal relationship with the study drug
- Stops/improves when the study drug has been stopped
- Can reasonably be explained by known characteristics of the drug

Probable:

- Reasonable temporal sequence from the study drug administration
- Stops/improves when the study drug has been stopped
- Event cannot easily be explained by subject's clinical state or other factors

Possible:

- Reasonable temporal relationship with the study drug
- Event could have been produced by the subject's clinical state or other factors

Unlikely:

- Poor temporal relationship to the study drug
- Subject's clinical state is likely to have an association with the effect

Unrelated:

- Definitely not associated with the study drug administered

Events that are assessed as "definite", "probable" and "possible" in relation to study treatment are regarded as AEs that cannot be denied a causal relationship to the study drug and will be handled as "related to study drug" for reporting purposes. Events that are assessed as "unlikely" or "unrelated" to study treatment will be handled as "not related to study drug" for reporting purposes.

6.6.4 Reporting of Adverse Events

All AEs, regardless of severity and whether or not they occurred during the treatment or follow-up period, are to be recorded on the appropriate AE pages (either 'serious' or 'non-serious') in the eCRF. The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, relationship to study drug. Each event should be recorded separately.

Any signs and symptoms that occur after obtaining the informed consent and receiving one HBI-8000 or nivolumab dose of treatment will be described as AEs and graded according to the CTCAE in the AE section of the eCRF. All AEs that are collected after the first dose of either HBI-8000 or nivolumab to the End-of-Study assessment will be recorded on the eCRF.

Abnormal laboratory test values that are **not** considered clinically significant by the Investigator will be recorded only on the laboratory section of the eCRF and not in the AE section. However, abnormal laboratory test results considered clinically significant by the Investigator are to be recorded in the AE section of the eCRF in addition to the laboratory section. Abnormal laboratory results that meet the definition of an SAE should also be reported on an AE/SAE form. Relationship (i.e., reasonable causal relationship) to study drug treatment and countermeasures taken will be noted on the eCRF.

Disease progression should **not** be recorded as an AE. Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, will not be reported as an AE, but the procedure and/or therapeutic treatment should be recorded on the appropriate eCRF. The medical condition for which the procedure was performed must also be reported.

6.6.4.1 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Adverse events classified as "serious" require expedited reporting to comply with regulatory requirements. All AEs that are serious, unexpected, and associated with the use of HBI-8000 will be reported to the regulatory authorities in accordance with the Guideline for Industry International Conference on Harmonization (ICH) E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

In case of Serious and Unexpected Suspected Adverse Reactions (SUSARs) the Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report any suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event [21 Code of Federal Regulations (CFR) 312.32(c)(1)(2)]:

Fatal or life threatening SUSARs:

- Not later than **7 calendar days** after the Sponsor has information that the case reported fulfills the criteria for a fatal or life-threatening SUSAR, with any follow up information to be reported within a **further 8 calendar days**.

All other SUSARs:

- Not later than **15 calendar days** after the Sponsor has information that the case fulfilled the criteria for a SUSAR.

All SAEs must be recorded in the eCRF within 24 hours of Investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor's authorized representative must be made within 24 hours, irrespective of the extent of available AE information. In case the eCRF cannot be used by the Investigator to generate the SAE/Pregnancy form, a paper SAE/Pregnancy form will be used and will be faxed to the Sponsor's authorized representative. Once the eCRF limitation is resolved, the Investigator should enter all the information from the paper report into the eCRF as soon as possible.

This timeframe also applies to additional new information (i.e., follow-up) on previously forwarded SAE reports. For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor's authorized representative in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor's authorized representative to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor's authorized representative. All SAEs requiring expedited regulatory reporting will be evaluated, summarized, and reported to Investigators.

Investigators will be notified by the Sponsor's authorized representative of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor's authorized representative. The Sponsor's authorized representative will ensure that all SAEs are reported to the appropriate regulatory authorities.

6.6.5 Follow-Up of Adverse Events

Any signs and symptoms that occur after receiving one HBI-8000 or nivolumab treatment dose post informed consent, should be documented as an adverse event. Subjects should be asked to specifically describe any signs, symptoms, or AEs (regardless of relationship to therapy) they may notice. At a minimum, subjects should be asked to report AEs at each visit to the study center. Conditions that the subject experienced prior to informed consent should be recorded in the medical history section of the eCRF.

All AEs (including SAEs), regardless of their relationship to study drug or study procedure, will be collected after the subject signs the informed consent and receives one HBI-8000 or nivolumab treatment dose through the EoT Safety Follow-up visit.

AEs, Grade 2 and above, considered to be at least possibly related to the study drug must be followed up after the EoT assessment until the events have resolved, returned to the baseline level, or are judged by the Investigator to be stabilized or that further follow-up is not required, unless the subject is withdrawn from the study due to initiation of new therapy or consent withdrawal for further follow-up. AEs that are assessed by the Investigator as unrelated to study treatment will be followed only to the EoT visit. The outcome of any AEs which do not resolve will be recorded as "ongoing" on the eCRF.

6.6.5.1 Extended Phase 2 Secondary Objectives: Adverse Effects and Efficacy

Once RP2D is identified, up to 100 additional subjects with melanoma or NSCLC who are evaluable for efficacy will be enrolled in the extended phase of this study, for a minimum of 20 subjects evaluable for efficacy treated at RP2D for each disease indication, (e.g., melanoma CPI-untreated), to confirm the safety and explore efficacy of HBI-8000 at RP2D combined with nivolumab in the study subject population. More specifically, in this extended phase, additional data on possible DLT, frequency and severity of adverse effects, and efficacy will be obtained. At the end of this extended phase, the DLT rate, the adverse effect rate, and the response rate will be calculated.

6.6.5.2 HBI-8000 Potential Toxicity

From the results of completed clinical studies of HBI-8000 with more than 290 subjects enrolled, monotherapy exhibited good safety, tolerance, and compliance. The clinical trials conducted showed that the toxic reactions of HBI-8000 monotherapy or combination therapy with chemotherapeutic drugs were mainly hematological system reactions, gastrointestinal reactions, and systemic reactions, which manifested as decreased blood cells, digestive system reactions and fatigue. Hematologic toxicity can be immediately identified by regular routine blood test and controlled by dose reduction and/or symptomatic treatment. The digestive system reactions and fatigue caused by HBI-8000 were usually mild and did not affect continuous medication. Toxic reactions in other systems occur less frequently, are less severe and are controllable.

When used in combination with paclitaxel and carboplatin in Chinese subjects, HBI-8000 did not appear to increase the toxicity of chemotherapeutic drugs. It was observed during the Phase 1b clinical trial of HBI-8000 in combination with paclitaxel and carboplatin to treat NSCLC that HBI-8000 exerted no effect on the in vivo PK parameters of paclitaxel (substrate of CYP3A4). Paclitaxel or carboplatin did not affect the in vivo PK parameters of HBI-8000. A Phase 2 double-blind, placebo-controlled trial in combination with paclitaxel and carboplatin in NSCLC is completed and in the analysis phase. Please refer to Investigator's Brochure for current information.

6.6.5.3 Nivolumab

The Investigator should be experienced in the use of nivolumab and familiar with the nivolumab prescribing information provided by the manufacturer. Additional information regarding the use of nivolumab in combination with other agents can be found in the OPDIVO® Full Prescribing Information [OPDIVO®(nivolumab) USPI, 2020].

If an irAE is suspected, a thorough evaluation should be conducted in an effort to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity. All irAEs are graded according to the CTCAE, v4.03.

If guidelines for an irAE are not specified below, nivolumab should be held for any Grade ≥3 irAE and can be resumed for subjects whose irAEs recover to Grade ≤2, after discussion with Sponsor as well as resuming treatment once steroid dose has been tapered over at least 1 month to physiological dose of 10 mg prednisone equivalent or less per day. Systemic corticosteroids (1 to 2 mg/kg/day) are indicated for all Grade 3 or Grade 4 irAEs if not otherwise specified as

below. Steroid should be tapered once symptoms improve to Grade 2 or less and tapered over at least 1 month.

Nivolumab should be permanently discontinued for:

- Life-threatening or Grade 4 AE,
- Any severe or Grade 3 treatment-related adverse reaction that recurs,
- Inability to reduce corticosteroid dose to ≤10 mg of prednisone or equivalent/day within 12 weeks,

There are no recommended dose modifications for hypothyroidism or hyperthyroidism. In the event that nivolumab is discontinued, HBI-8000 would be continued until one of the conditions for HBI-8000 discontinuation is met (see Section 3.3).

Dose modifications for nivolumab are in Table 4.

Table 4: Recommended Dose Modifications for Nivolumab

Adverse Reaction	Severity	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose *
	Grade 3 diarrhea or colitis	Withhold dose
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose *
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose *
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose *
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose *
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose *
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose *
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Rash	Grade 3 rash	Withhold dose *
	Grade 4 rash	Permanently discontinue
Encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose *
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction	
	First occurrence	Withhold dose *
	Recurrence of same Grade 3 adverse reactions	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue**

* Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

** Medically stable Grade 2 AEs controlled by prednisone ≤10 mg per day (or equivalent) or thyroid replacement may resume nivolumab at Investigator's discretion.

Interrupt or slow the rate of infusion in subjects with mild or moderate infusion reactions.

Discontinue nivolumab in subjects with severe or life-threatening infusion reactions. [OPDIVO®(nivolumab) USPI, 2020]

Table 5: Nivolumab Warnings and Precautions

Event	Action to Be Taken
Immune-mediated pneumonitis	Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis.
Immune-mediated colitis	Nivolumab as a single agent: Withhold for moderate or severe and permanently discontinue for life-threatening colitis.
Immune-mediated hepatitis	Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation.
Immune-mediated endocrinopathies	Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed.
Immune-mediated nephritis and renal dysfunction	Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation.
Immune-mediated rash	Withhold for severe and permanently discontinue for life-threatening rash.
Immune-mediated encephalitis	Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis.

6.6.6 Clinical Laboratory Evaluations

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

Abnormal laboratory test values that are **not** considered clinically significant by the Investigator will be recorded only on the laboratory section of the eCRF and not in the AE section. However, abnormal laboratory test results that require study drug modification or other treatment or considered clinically significant by the Investigator are to be recorded in the AE section of the eCRF in addition to the laboratory section. Abnormal laboratory results that meet the definition of an SAE should also be reported on an AE/SAE form. Relationship (i.e., reasonable causal relationship) to study drug treatment and countermeasures taken will be noted on the eCRF.

6.6.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 6.6.4).

6.6.8 Independent Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) consisting of three independent therapeutic experts in oncology, as well as a biostatistician has been commissioned and charged with the responsibility of evaluating cumulative safety and clinical trial data at regular intervals. As such, the primary objective of the DSMB is to monitor the safety of the subjects enrolled and to be enrolled in the study described in DSMB Charter, as well as on an ad hoc basis, as needed. Four

DSMB reviews have been completed, and it was determined that further reviews are no longer needed as safety profiles have been confirmed with expanded Phase 2 cohorts.

7 STATISTICAL METHODS

7.1 General Statistical Considerations

Protocol HBI-8000-302 is an open-label, Phase 1b/2 study evaluating HBI-8000 in combination with nivolumab in subjects with advanced melanoma, RCC, and NSCLC. The objectives of this study are to determine the safety, tolerability, MTD or RP2D, PK, pharmacodynamics, and preliminary anti-tumor activity of HBI-8000.

Statistical analyses of safety, tolerability, and anti-tumor activity will be primarily descriptive in nature, as the goal of the study is to determine the DLTs, MTD, and/or RP2D of HBI-8000 to be used for further investigation in combination with standard dose and regimen of nivolumab. This goal will be achieved by the results of a deterministic algorithm; thus, statistical hypothesis testing is neither intended nor appropriate within this context. To this aim, categorical variables will be summarized by frequency distributions (number and percentages of subjects), continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, and time-to-event variables will be summarized using Kaplan-Meier methods and figures for the estimated median time.

All data collected will be presented in subject listings and will be summarized by HBI-8000 dose level received. All analyses, summaries, and listings will be performed using SAS software (version 9.3 or higher).

A detailed methodology for summary and statistical analysis of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP) that will be dated and maintained by HUYABIO. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

7.2 Determination of Sample Size

Based on the assumption of 3 dose levels tested, it is anticipated that up to 18 subjects will be enrolled in the dose escalation phase of this study. Per the standard 3+3 Phase 1 dose escalation design, the total number of subjects to be enrolled cannot be precisely determined as the sample size is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD of HBI-8000. Each subject will participate in only 1 dose level cohort.

Once the MTD and/or RP2D has been established, up to 20 subjects may be enrolled at this dose level to further characterize safety and allow for preliminary evidence of efficacy activity in specific patient population of interest. With a sample size of 20 subjects the probability is high (87.8%) that an adverse event with at least a 10% incidence will be detected in at least one subject (Table 6). Obtaining this information will help in planning for future immuno-oncology studies.

Table 6: Probability of Detecting AEs that Occur at Various Frequencies

True Frequency of AE	Probability of Detecting at Least 1 AE in 20 Subjects
1%	18.2%
5%	64.2%
10%	87.8%
15%	96.1%
20%	98.8%
25%	99.7%
30%	>99.9%

7.3 Treatment Assignment and Blinding

This is an open-label, dose-escalation, sequential enrollment study; therefore, no randomization or blinding procedures will be performed.

7.4 Replacement of Subjects

Subjects who are lost to follow up or withdraw consent for study participation prior to receiving HBI-8000 or who withdraw in Cycle 1 for reasons unrelated to drug toxicity may be replaced.

7.5 Populations for Analysis

7.5.1 Safety Population

The Safety analysis population will include all subjects who receive at least one dose of HBI-8000. The safety analyses population will be the primary population for evaluating treatment administration / compliance and safety in the study.

7.5.2 Efficacy Population

The full analysis population consists of all subjects meeting all eligibility criteria who receive at least one dose of HBI-8000, have at least one post-baseline assessment of efficacy, or who discontinue study early due to clinical PD. The protocol specified population for efficacy consists of subjects meeting all eligible criteria, having received at least 2 cycles of HBI-8000, with at least 1 imaging study to evaluate disease status after completing 2 cycles of treatment. Both populations will be analyzed and reported. For subjects who do not meet disease-specific eligibility criterion (e.g., not having melanoma, NSCLC, or RCC) or do not have any disease assessment after receiving study treatment will not be evaluable for efficacy.

7.5.3 PK and Pharmacodynamics Populations

All subjects who have at least one blood sample providing evaluable PK and/or pharmacodynamic data for HBI-8000.

7.6 Subject Disposition

Data tabulations will summarize the following subject numbers:

- Enrolled
- HBI-8000 treatment dose received
- Evaluable for safety and efficacy
- Protocol violations
- Protocol completions
- Withdraw from study due to:
  - Adverse event
  - Investigator's discretion
  - Withdrawal of consent
  - Lost to Follow-up
  - Other reasons as collected on the case report form
  - Death

7.7 Subject Characteristics

Demographic and baseline characteristics of subjects will be summarized using descriptive statistics:

- Age
- Gender
- Race
- Ethnicity
- ECOG Performance Status
- Prior therapies
- Stage of Disease
- Tumor characteristics when available: PD-L1 level (with test name), BRAF mutation (melanoma), EGFR mutation and ALK translocation (NSCLC), tumor mutation burden (with test method)
- Other baseline characteristics as collected on the eCRF

7.8 Concomitant Medications

The number and proportion of subjects using different concomitant medications will be tabulated and summarized by World Health Organization (WHO) Drug anatomical therapeutic chemical (ATC) classification and preferred term.

7.9 Treatment Administration / Compliance

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

7.10 Efficacy Analyses

The efficacy data cut-off for the main study will occur when the last subject receiving HBI-8000 has been monitored for tumor response for at least 12 months or all subjects have shown disease progression, whichever is earlier. Data obtained up to the main cut-off date will be analyzed for overall efficacy.

The efficacy endpoints are the following:

- **Objective Response Rate (ORR),** defined as the percent of subjects with CR or PR according to RECIST v1.1 and iRECIST criteria, relative to the efficacy population. Subjects who do not have an on-study assessment due to safety issues will be included as non-responders.
- **Disease Control Rate (DCR),** defined as the percent of subjects with CR, PR, or SD according to RECIST v1.1 and iRECIST criteria, relative to the efficacy population.
- **Clinical Benefit Rate (CBR)**, defined as the percent of subjects with a CR, PR, or SD lasting for at least 12 weeks according to RECIST v1.1 and iRECIST criteria, relative to the efficacy population.
- **Duration of Response (DoR),** defined as the time from documentation of tumor response to disease progression.
- **Progression-Free Survival (PFS),** defined as the time from the start of treatment (Day 1 Cycle 1) until objective tumor progression or death.

The Safety visit is scheduled on 30 ± 3 days after the last dosing of the HBI-8000 or before the initiation of new cancer treatment, whichever is earlier.

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% CI.

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

7.11 Safety Analysis

All subjects who receive at least one dose (any amount) of HBI-8000 will be included in the summaries and listings of safety data. Overall safety profile and tolerability will be characterized by type, frequency, severity, timing, duration and relationship of study therapy of adverse events and laboratory abnormalities.

Safety data cut-off for the main study will occur after efficacy data cut-off and include End of Treatment safety visit and applicable safety follow-up based on assessment at EoT. Once all subjects in Extension Phase discontinue receiving HBI-8000 and complete EoT assessment, Extension Phase safety data will be integrated with the safety data from the main study and analyzed for overall safety of the study. The final analysis of safety for the entire study is planned at 3 months after the last subject discontinues study treatment.

7.11.1 Adverse Events

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system version 18.0 or higher. The severity of the toxicities will be graded according to the NCI-CTCAE v4.03.

In all summaries, emphasis will be placed on treatment emergent adverse events (TEAEs), namely, those with initial onset or that worsen in severity after the first dose of HBI-8000. Adverse events will be summarized by the frequency of subjects experiencing TEAEs corresponding to body systems and MedDRA preferred term and by worst NCI-CTCAE v4.03 Grade. Summaries will also be provided of treatment related TEAEs, namely, those judged by the Investigator to be related or likely related to HBI-8000.

AEs resulting in discontinuation of HBI-8000 treatment or withdrawal from the study, Grade 3 or higher, SAEs, and deaths on-study will be tabulated.

All DLTs will be reported and the MTD and/or RP2D identified.

7.11.2 Laboratory Tests

Laboratory data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes from baseline (the value obtained prior to dosing on Day 1 of Cycle 1) using descriptive statistics.

For those analytes with CTCAE grades, abnormal laboratory values will be summarized by dose group and overall by shift tables displaying numerical values and percentages classified by Baseline Grade (i.e., Grade prior to dosing on Day 1 of Cycle 1) and maximum Grade on treatment. All laboratory data will be presented in listings.

7.11.3 Safety ECGs

Baseline and serial ECGs will be performed to evaluate the potential effects of the study drug on the heart. The ECG parameters (PR interval, QRS duration, QT, and QTcF) will be summarized descriptively by dose cohort and overall for each time point for both the observed values and the change from Baseline to each post-baseline time point. The number and percentage of subjects with QT or QTc (QTcF) outlier values (at any post-baseline time point), as defined in ICH E14, will be summarized.

7.11.4 Vital Signs and Physical Findings

Vital signs data will be summarized by the observed value at each scheduled assessment, together with the corresponding changes from Baseline using descriptive statistics.

Physical findings will be presented in data listings.

7.12 Interim Analysis

No interim analysis for efficacy is planned for this Phase 1b/2 study.

7.13 Main Study and Extension Phase Analysis

The efficacy and safety analyses will be based on the data obtained at the cut-off date for Main study. Safety data from Extension phase will be incorporated to total safety data based for the entire study.

7.14 Population PK Analysis

PK data collected in this study will be combined with PK data collected from other studies and a POPK analysis will be performed. Results of the POPK analysis will be presented in a report separate from the Clinical Study Report (CSR).

7.15 Pharmacodynamic Analysis

7.15.1 PBMC Acetylation

Histone acetylation levels will be presented by listings and descriptive summary statistics separately by dose, time over the course of treatment (Phase 2 only).

7.15.2 QTC Interval Analysis (Holter 12-Lead ECGs)

Observed and change-from-baseline QTc and other ECG intervals and the Investigator interpretation of the ECGs will be summarized at each scheduled assessment. The incidence of clinically noteworthy QTc intervals will be tabulated. A statistical assessment of the relationship between QTc and PK concentrations will be carried out using data from multiple studies and presented in a separate report. All analyses of ECG intervals will be based on the mean of the replicate ECGs at each assessment (Phase 1b only).

8 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (GCP) (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Central laboratories for clinical laboratory parameters and ECGs
- Center Initiation visit
- Early center visits post-enrollment
- Routine center monitoring
- Ongoing center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report
- The Investigator shall verify, by signature, the integrity of the data transmitted to the Sponsor

In addition, the Sponsor or its representative may conduct periodic audits of the study processes, including, but not limited to study center, center visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

8.1.1 Monitoring

The Sponsor has engaged the services of a Contract Research Organization (CRO), IQVIA to perform all monitoring functions within this clinical study. CRO monitors will work in accordance with CRO's SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study center. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). For the following items, this check will be 100%:

- Subject identification number
- Subject consent obtained
- Subject eligibility criteria (inclusion and exclusion criteria)
- Medical record of AE
- Efficacy variables

8.1.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of the Sponsor and CRO.

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, electrocardiogram (ECG) results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using MedDRA version 18.1. Concomitant medications will be coded using WHO-drug dictionary enhanced (DDE). Concomitant diseases/medical history will be coded using WHO DRUG DDE.

8.1.3 Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of investigational medicinal product, including eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8.1.4 Quality Assurance Audit

Study centers, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or CRO on behalf of Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

8.1.5 Site Audits

The Principal Investigators or Sub-Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the Principal Investigator or Sub-Investigator

agrees to allow the Sponsor, its representatives, or the regulatory agencies access to all study records.

The Investigator should promptly notify the Sponsor or its authorized representative of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or its authorized representative.

9 ETHICS

9.1 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (48th General Assembly, Somerset West, Republic of South Africa, October 2008 [or current version]), the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.2 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will provide the CRO with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study center(s). The Investigator should submit the written approval to Sponsor or representative before enrolment of any subject into the study.

The Sponsor or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the CRO (IQVIA) of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

The Sponsor or its representative will handle the distribution of any of these documents to the national regulatory authorities. The Sponsor or its representative will provide Regulatory Authorities, Ethics Committees and Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

Each Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. The Sponsor or its representative will provide this information to the Investigator so that he/she can meet these reporting requirements.

9.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated ICF.

9.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique subject identification number. Subject names are not included in data sets that are transmitted to any Sponsor location.

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the subject, unless permitted or required by law. Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare, for treatment purposes.

9.5 Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The Sponsor or its representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a Sponsor or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Regulatory authorities may also require access to the relevant files.

9.6 Protocol Amendments

Any changes that affect subject safety or welfare will be submitted to the IRB and regulatory authority (where applicable) for approval prior to implementation. The Investigator and the Sponsor must approve all amendments. No amendment will be implemented until approved and signed by all parties. Exceptions to this are when the Investigator considers subject safety to be compromised.

Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the protocol.

9.7 Study Closure

The Sponsor, its authorized representative, and the Investigator in his site have the right to close this study at any time. As far as possible, this should occur after mutual consultation. The IRB must be informed, if required by legislation.

Should the study be closed prematurely, all unused study drug will be reconciled with dispensing records, documented, and returned to the Sponsor. Alternatively, if directed by the Sponsor, unused drug (tablets) may be destroyed at the study center after completion of drug accountability by the site monitor.

The Sponsor will notify the Investigator(s) if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

9.7.1 Study Discontinuation

Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to study subjects
- Subject enrollment is unsatisfactory

9.7.2 Site Discontinuation

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for GCP

10 STUDY ADMINISTRATION

10.1 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

No records should be disposed of without the written approval of the Sponsor.

10.2 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow the Sponsor, its representatives, CRO, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

10.3 Investigator Information

10.3.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997); the US CFR Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.3.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page (see Appendix 10) and send a copy of the signed page to the Sponsor or its representative. By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

10.3.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

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12 APPENDICES

APPENDIX 1. SCHEDULE OF DOSING AND ASSESSMENTS

Visit	**Screen**	**BL**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**≥Cycle 5**		**EoT Safety visit[a]**	**Survival F/U**
Study Day	**-28 to -1**	**-7 to -1**	**1**	**15[b]**	**1[b]**	**15[b]**	**1[b]**	**15[b]**	**1[b]**	**15[b]**	**1[b]**	**15[b]**		
Time Window				(±1 day)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±1 week)
Informed consent[c]	X													
Medical History, Cancer Diagnosis (incl PD-L1 expression, BRAF, EGFR, ALK mutation status if available) and Treatment History, Baseline Conditions[d], Demographics, Height	X													
Vital signs[e]		X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam, Weight, ECOG Performance Status		X	X		X		X		X		X		X	
Pharmacodynamic 12-lead Holter ECG[f]		X[f]	X[f]											
Safety ECG[g]		X[g]					X[g]						X[g]	
Brain MRI[h]	X[h]													
Hematology[i]		X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation (PT/aPTT)[j]		X												
Serum Chemistry including LDH[k]		X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[l]		X											X	
Pregnancy test (if applicable)[m]		X											X	
Hepatitis B and C panel [n]	X													

Visit	Screen	BL	Cycle 1		Cycle 2		Cycle 3		Cycle 4		≥Cycle 5		EoT Safety visit[a]	Survival F/U
Study Day	**-28 to -1**	**-7 to -1**	**1**	**15[b]**	**1[b]**	**15[b]**	**1[b]**	**15[b]**	**1[b]**	**15[b]**	**1[b]**	**15[b]**		
PK blood samples (sparse sampling)[f, o]			X		X[t]		X[t]		X		X			
PBMC Histone Acetylation Plasma Cytokine/Chemokine (Phase 2 only)[p]		X			X		X		X				X	
Nivolumab infusion			X (Day 2 Phase 1b only)	X[q]	X	X[q]	X	X[q]	X	X[q]	X	X[q]		
HBI-8000 PO BIW			X											
Tumor assessment[r]	X		Day 1 of Cycles 3, 5, 7, etc. (±3 days) (every 8 weeks) until PD											
Adverse events			X	X	X	X	X	X	X	X	X	X	X	
Treatment Compliance			X	X	X	X	X	X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor status and first anti-cancer tx[s]														X
Immune correlative Sub-study[t] (Phase 2 only)		X		X	X		X		X[t]					

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BIW, twice weekly; BL, Baseline; BUN, blood urea nitrogen; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report from; EoT, end-of-treatment; F/U, follow-up; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cells; PD-L1, programmed death-ligand 1; PK, pharmacokinetic; PO, by mouth; PD, progressive disease; PT, prothrombin time; QTc, QT interval corrected by heart rate; TSH, thyroid stimulating hormone; tx, treatment; free T4, free thyroxine; total T3, total triiodothyronine.

a End-of-Treatment Safety Follow-Up visit, performed 30±3 days after the last day of HBI-8000 administration or before the initiation of new cancer treatment, whichever is earlier. Subjects who will enter Extension Phase for continued HBI-8000 treatment will have their EoT deferred until they discontinue their Extension Phase treatment. The EoT safety assessments will then be conducted 30 (±3) days after the last dose of Extension Phase treatment.

b All visits and assessments after Cycle 1 Day 15 onwards may be performed ±3 days to accommodate unforeseen delays, holidays, or vacations. Phase 2 portion for ≥Cycle 3, Day 15 visit is required if patient receives nivolumab on an every 2-week schedule or if the subject requires further follow up testing. When a Day 15 visit occurs, vitals, hematology, chemistry, adverse events, treatment compliance and concomitant medication review are required assessments.

c Study consent must be performed prior to initiation of any study-specific procedures.

d Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.

e Heart rate, diastolic and systolic blood pressure after subject is in a supine position for 5 minutes. On days when ECGs are taken, vital signs should be taken prior to the ECG recording. During Cycle 1 vital signs should be measured on Days 1 and 2. In Phase 2 portion, ≥Cycle 3 Day 15 vitals required only if there is subject visit.

f For the QTc substudy (Phase 1b only), continuous Holter ECG will be recorded from 1 hour prior to breakfast until 4 hours post-dose on Cycle 1 Day 1. All other procedures should be avoided during Holter monitoring time. On the Baseline day, the recording time will be clock time-matched to the recording time on Cycle 1 Day 1. ECG measurements will be extracted from these recordings according to the schema shown in Appendix 2. Vital signs (heart rate, systolic and diastolic blood pressure) should be measured prior to the ECG recording, after the subject has been in a supine position for at least 5 minutes. ECG recordings and vital signs should be performed directly before PK sampling time points.

g The ECG measurements done on these visits are for safety assessment purposes.

h As clinically indicated if no documented brain metastasis.

i Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count. In Phase 2 portion, ≥Cycle 3 Day 15 lab required only if there is subject visit.

j Coagulation (PT/ INR, aPTT).

k BUN, creatinine, AST, ALT, LDH, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, TSH, total T3, T4 free (direct), total protein, albumin, uric acid, alkaline phosphatase, sodium, potassium, calcium, magnesium, phosphorus and glucose. In Phase 2 portion, ≥ Cycle 3 Day 15 lab required only if there is subject visit

l Urinalysis: dipstick followed by microscopic examination if abnormal results.

m Only for women of childbearing potential. Serum pregnancy test at baseline (within 7 days of starting treatment) and at the end-of-treatment.

n HBsAg, anti-HCV antibodies **or** HCV RNA.

o PK blood sampling will be done according the schema shown in Appendix 2 and Appendix 3. In Phase 2 cohort expansion, only selected sites will participate.

p Phase 2 only. Sample timepoints: at baseline (The BL sample must be collected prior to any treatment and may occur Cycle 1 Day 1 pre-dose), then Day 1 of cycles 2, 3 and 4 before study drugs administration.

q Phase 1b: dosing is 240 mg Nivolumab infusion. Phase 2: Dosing every 2 weeks or 4 weeks per Opdivo Package Insert and Appendix 9.

r Main Study: Tumor assessment of all lesions by radiographic or other modality (CT, MRI); Tumor assessments to be performed at screening, Day 1 of Cycles 3, 5, 7, etc. (± 3 days) every 8 weeks until PD.

s Main Study: Tumor assessment data will be collected every 12 (±1) weeks after End-of-Treatment (e.g., last dose of HBI-8000) if PD has not been recorded until PD, initiation of new anti-cancer treatment, or referral to hospice for up to 12 months after the last dose of HBI-8000 or the end of the main study. First anti-cancer treatment should be recorded. Extension Phase: tumor response will be based only on reports by investigator as PD, SD, PR and CR at intervals according to standard of care.

t When blood sampling occurs on the same day for PBMC histone acetylation and immune correlative sub-study, follow instruction in Appendix 8. The last time point is at time of PD or EoT visit whichever is earlier.

APPENDIX 2. POPULATION PHARMACOKINETICS (PK) SAMPLING AND 12-LEAD HOLTER ECG (PHARMACODYNAMIC) MEASUREMENT SCHEMA (PHASE 1B)

Phase 1b PK sample collection and pharmacodynamic ECG measurements should be done at the following times:

Visit	Time Points	PK	QTc[a]
Baseline Holter ECG Day (-7 to -1)[b]	Predose (0.5 hour prior to breakfast)[c]		X
	Dose (mock dose, ~30 min after breakfast)=time 0		
	Postdose 1h ± 15 min		X
	2h ± 15 min		X
	3h ± 15 min		X
	4h ± 15 min		X
Cycle 1 Day1 (C1D1)	Predose (0.5 hour prior to breakfast)[c]	X	X
	Dose HBI-8000 ~30 min after breakfast = time 0		
	Postdose[d] 1h ± 15 min	X	X
	2h ± 15 min	X	X
	3h ± 15 min	X	X
	4h ± 15 min	X	X
	5h ± 30 min	X	
	7h ± 30 min	X	
Cycle 1 Day 2 (C1D2)	24h ± 4 h	X	
Cycle 2 Day 1 (C2D1)	Predose[c]	X	
	Dose HBI-8000 ~30 min after breakfast = time 0		
	Postdose[e, f] 1h ± 15 min	X	
	2h ± 15 min	X	
	3h ± 15 min	X	
	4h ± 15 min	X	
	5h ± 30 min	X	
	7h ± 30 min	X	
Day 1 of subsequent cycles	Predose[c]	X	

Note: When PK samples and ECG measurements are scheduled at the same time, the ECG measurement should always be performed first, followed by the PK sample. On each ECG measurement day, after breakfast is completed, no food or drink should be administered (except water) until after the 4-hour post-dose Holter ECG extraction time is completed. Phase 1b only.

a Measurements on the Baseline ECG day should be matched to the clock time of the measurements on Day 1 of Cycle 1.

b Triplicate ECGs will be extracted from the continuous Holter ECG recordings at these time points. Subjects must rest in a supine position for approximately 15 minutes prior to each time point.

c Pre-dose is before the subject receives any study drug (at Baseline, this is prior to a mock dose approximately 30 minutes after breakfast). Only for baseline Day and C1D1, this time point occurs before breakfast, in order to accommodate ECG measurement.
d After the subject receives HBI-8000 (for this cycle only, the subject will receive nivolumab on C1D2, after collection of the 24-hour PK sample).
e After the subject has received both study drugs.
f These times are relative to HBI-8000 dosing.

APPENDIX 3. POPULATION PHARMACOKINETICS (PK) AND PHARMACODYNAMICS SAMPLING AND SCHEMA (PHASE 2)

Phase 2 PK and pharmacodynamic sample collection should be done at the following times:

Visit	Time Points	PK	PBMC Histone Acetylation[d]
Cycle 1 Day1 (C1D1)	Predose (0.5 hour prior to breakfast) Dose HBI-8000 ~30 min after breakfast = time 0 Postdose[a] 1h ± 15 min 2h ± 15 min 3h ± 15 min 4h ± 15 min 5h ± 30 min 7h ± 30 min	X X X X X X X	
Cycle 2 Day 1 (C2D1)	Predose Dose HBI-8000 ~30 min after breakfast = time 0 Postdose[b, c] 1h ± 15 min 2h ± 15 min 3h ± 15 min 4h ± 15 min 5h ± 30 min 7h ± 30 min	X X X X X X X	X[d]
Day 1 of subsequent cycles	Predose	X[e]	X[d]

Note: In Phase 2 cohort expansion, only selected sites will participate.

a After the subject receives HBI-8000 (for this cycle only, the subject will receive nivolumab on C1D1 after collection of the last PK sample). Subjects are not required to return to clinic on Cycle 1 Day 2 to receive nivolumab and 24-hour PK sampling.

b After the subject has received both study drugs.

c These times are relative to HBI-8000 dosing.

d Sample time points: at baseline, then Day 1 of Cycles 2, 3 and 4 before study drugs administration.

e PK predose sample for subsequent Day 1 of subsequent cycles ≤Cycle 12

APPENDIX 4. PERFORMANCE SCALES: KARNOFSKY AND ECOG SCORES CONVERSION

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death not imminent	30	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Dead	0	5	Dead

Source: [Oken et al., 1982]

APPENDIX 5. COLLECTION OF SAMPLES FOR HISTONE ACETYLATION AND CYTOKINE/CHEMOKINE ANALYSIS

As with any protein product, minimization of processing time is essential –acetylated histone H3 (acH3), acetylated histone H4 (acH4) and cytokines will degrade if the samples are not processed in a timely manner.

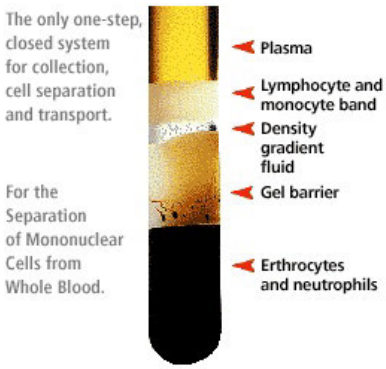
Materials & Equipment:

1. BD Vacutainer CPT Mononuclear Cell Preparation Tube – Sodium Citrate (4 mL, Cat No. 362760 or 8 mL, Cat No. 362761)
2. Centrifuge with swinging bucket rotor and tube carriers/adapters for 13 x 100 mm (4-mL CPT tubes) or 16 x 125 mm (8-mL CPT tubes) tube size
   - Centrifuge must be capable of generating at least 1500 RCF (G-force) at tube bottom
3. 10 mL or 15-mL conical centrifuge tubes, sterile
4. Sterile PBS or HBSS buffer

Procedure:

The BD Vacutainer® CPT™ Tube with Sodium Citrate should be at room temperature (18°C to 25°C)

1. Collect blood into the tube using the standard technique for BD Vacutainer Collection Tubes
2. After collection, store tube upright at room temperature until centrifugation
3. Blood samples should be centrifuged within two hours of blood collection for best results
4. Remix the blood sample immediately prior to centrifugation by gently inverting tube 8 to 10 times
5. Centrifuge tube/blood sample at room temperature (18°C to 25°C) in a horizontal rotor (swing-out head) for a minimum of 15 minutes at 1500 to 1800 Relative Centrifugal Force (RCF)
6. Remove tubes from centrifuge and observe the position of the gel barrier and blood components; The plug should be above the red cell fraction and below the plasma/monocyte fraction



7. Remove the stopper and aspirate most of the plasma fraction without disturbing the monocyte band
8. Transfer plasma equally into prelabeled NUNC tubes, cap the tube and freeze at -80°C

9. Fill the tube with PBS or HBSS buffer, mix by gently pipetting back and forth 4 to 5 times, and remove the now suspended cells (PBMC), transferring them to a fresh, sterile 10-mL or 15-mL conical tube
10. Top up the tube with PBS/HBSS and centrifuge at 1000 RCF for 10 minutes
11. Carefully aspirate most of the buffer, gently resuspend the cells and add fresh buffer
12. Centrifuge at 1000 RCF for 10 minutes
13. Carefully aspirate all of the buffer, being careful to not disturb the pellet
14. Cap the tube and freeze at -80°C

APPENDIX 6. STRONG CYP3A4 INHIBITORS

CYP3A Inhibitors - Strong
boceprevir
clarithromycin
conivaptan
grapefruit juice
indinavir
itraconazole
ketoconazole
lopinavir/ritonavir
mibefradil
nefazodone
nelfinavir
posaconazole
ritonavir
saquinavir
telaprevir
telithromycin
voriconazole

Taken from FDA Guidance on Drug−Drug Interactions, "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers":

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers (05Oct2022)

APPENDIX 7. RESPONSE CRITERIA COMPARISON

	RECIST v1.1 [Eisenhauer et al., 2009]	iRECIST [Seymour et al., 2017]
Lesion Measurement	Unidimensional	Unidimensional
Baseline Lesion Size	≥10 mm	≥10 mm
Baseline Lesion Number	5 lesions total, 2 per organ	5 lesions total, 2 per organ
Appearance of New Lesions	Always represents PD	iUPD
Response	CR = disappearance of all lesions	CR = disappearance of all lesions
	PR ≥30% decrease from baseline STD	PR ≥30% decrease from baseline STD
	SD = when neither PR nor PD can be established	SD = when neither PR nor PD can be established
	PD ≥20% increase in the nadir of STD (minimum 5 mm)	PD ≥20% increase in the nadir of STD (minimum 5 mm)
Confirmation after first assessment	Yes, if response is primary endpoint	Yes 8 weeks

CR = complete response; iRECIST = Immune-related Response Evaluation Criteria in Solid Tumors; iUPD = immune unconfirmed progressive disease; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; STD = sum of target lesion(s) diameter(s).

iRECIST defines immune unconfirmed progressive disease (iUPD) on the basis of RECIST v1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST v1.1) in lesion categories that had not previously met RECIST v1.1 progression criteria. However, if progression is not confirmed, but instead tumor shrinkage occurs (compared with baseline), which meets the criteria of immune complete response (iCR), immune partial response (iPR), or immune stable disease (iSD), then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for immune confirmed progressive disease (iCPD) to be assigned. If no change in tumor size or extent from iUPD occurs, then the timepoint response would again be iUPD.

APPENDIX 8. LIST OF BIOMARKER STUDIES

Test	Time points	Clinical Material	Participating sites	Patient population
Histone acetylation	Pre-treatment/BL*, C2D1, C3D1, and C4D1	PBMC-frozen	all	all
Cytokine/Chemokine multi-plex	Pre-treatment/BL*, C2D1, C3D1, and C4D1	Plasma-frozen	all	all
Checkpoint inhibitor response predictor -RNA transcript	Pre-treatment, C1D15, C2D1, C3D1, and EoT/PD	Whole blood-frozen	all	all
FACS immune cell response profile	Pre-treatment, C1D15, C2D1, C3D1, and EoT/PD	PBMC-fresh	Moffitt	Melanoma
NanoString Tumor tissue gene expression profiling	Pre-treatment, early treatment (C1D15 or C2D1), and EoT/PD	Biopsy	all	Melanoma (selected subjects)

EoT = End of Treatment; FACS = fluorescence activated cell sorting; PBMC = peripheral blood mononuclear cells; PD = Progressive Disease; RNA = ribonucleic acid.
* Sample must be collected prior to any treatment and may occur Cycle 1 Day 1(C1D1) pre-dose.

Sample preparation procedures:
Processing time is critical and should be done within 2 hours after collection of blood samples.

Histone Acetylation PBMC Processing — See Appendix 5 for details.
Cytokine/Chemokine Multi-Plex Plasma Processing — See Appendix 5 for details.

Checkpoint Inhibitor Response Predictor---RNA Transcript
Blood collection to be done prior to treatment at BL, C1D15, C2D1, C3D1, and EoT/PD in PAXgene® Blood RNA Tube, BD Biosciences, San Jose, CA, Cat#762165.

A) This should be the last tube of blood drawn in the series or a discard tube should be drawn.
B) Hold PAXgene tube vertically below the blood donor's arm during collection, collect the full 2.5 mL per tube.
C) After blood draw, gently invert the PAXgene tube 8 to 10 times.
D) Store tube upright at room temperature for 2 hours (minimum) to 72 (maximum) hours.
E) Freeze tubes at -20°C to -80°C and ship to Core Diagnostics for processing.
Attn: Receiving
Core Diagnostics, Inc.
3535 Breakwater Ave.
Hayward, CA 94545
Phone: 650-532-9513

FACS Immune Cell Response Profile (Moffitt)

Blood collection to be done prior to treatment at BL, C1D15, C2D1, C3D1, and EoT/PD. Collection tube BD Vacutainer® CPT Mononuclear Cell Preparation Tube – Sod. Citrate (4 mL, Cat No. 362760 or 8 mL, Cat No. 362761)

A) Processing of blood sample per Appendix 5, procedure steps 1 to 6, collection to be done within 2 hours post blood collection.
B) Transfer fresh PBMC samples to Moffitt core FACS facility for processing and analysis of immune components (TBD). Collect plasma and freeze for use in cytokine/chemokine multi-plex analysis.

NanoString Tumor Tissue Gene Expression Profiling (All sites, selected subjects)

Multiple serial biopsy to be taken at Pretreatment, early treatment (C1D15 or C2D1), and PD or end of treatment, whichever is earlier. Core needle biopsy is preferred but if necessary needle aspiration biopsy is acceptable.

A) Formalin-fix paraffin-embedded (FFPE) biopsy samples will be processed per standard FFPE protocol. These samples will be used for IHC and nanoString analysis.
B) FFPE biopsy samples will be shipped to Core Diagnostics for nanoString analysis.
C) IHC performed on FFPE samples will be determined on an as needed basis.

APPENDIX 9. OPDIVO® DOSING INFORMATION (PHASE 2)

Nivolumab dosing in Phase 2 will be conducted in accordance with the OPDIVO® Dosing Information of the Package Insert (March 2021).

The package insert recommends for melanoma, NSCLC and RCC intravenous infusion over 30 minutes until disease progression or unacceptable toxicity of OPDIVO® either as:

- 240 mg every 2 weeks *OR*
- 480 mg every 4 weeks

OPDIVO Dosing	Cycle Day of Administration
240 mg every 2 weeks	Day 1 and Day 15
480 mg every 4 weeks	Day 1

If Dosage and Administration Guidelines of the OPDIVO® package insert are further updated in the future, OPDIVO® Cycle Day administration in accordance with HBI-8000 dosing clarification may be provided via an HUYABIO International, LLC Protocol Administrative Letter.

APPENDIX 10. SIGNATURE OF INVESTIGATOR

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

PROTOCOL NO: **HBI-8000-302**

This protocol is a confidential communication of HUYABIO International, LLC. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from HUYABIO International.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name and address of the center in which the study will be conducted. Return the signed copy to Sponsor/CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____