Clinical Study Protocol

Protocol Title:	**A Phase 2b Open-Label Single Arm Study to Evaluate the Efficacy and Safety of Oral HBI-8000 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)**
Protocol Number:	**HBI-8000-203**
NCT Number:	**NCT02953652**
Version:	**6.0**
Date of Protocol:	**19 July 2021**
Sponsor:	**HUYABIO International, LLC**

HBI-8000-203 Protocol Synopsis

Name of Sponsor/Company:	**HUYABIO International, LLC**	
Study Drug:	**HBI-8000**	
Title of Study:	A Phase 2b Open-Label Single Arm Study to Evaluate the Efficacy and Safety of Oral HBI-8000 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)	
Protocol No:	HBI-8000-203	
Study site(s):	25 to 35 sites in Japan and 10 to 15 sites in South Korea	
Study duration: Approximately 66 months		**Phase:** 2b
Planned study period: 4Q 2016 (first patient in) to 3Q 2018 (last patient in) 2Q 2022 study completion		

Objectives:

Primary:

- To determine the efficacy of HBI-8000 administered twice a week (BIW) continuously

Secondary:

- To evaluate the safety and tolerability of HBI-8000 administered BIW continuously

Endpoints:

Primary:

- Objective response rate (ORR; Complete Response [CR] + Partial Response [PR])

Secondary:

- ORR by disease subtype (see inclusion criteria)
- Median duration of progression-free survival (PFS)
- Median duration of response (DOR)
- Safety

Exploratory:

- Median duration of overall survival (OS)
- Pharmacokinetics (selected sites)

Study Design:

This is a Phase 2b, open-label, non-randomized, single arm study to evaluate the safety, efficacy, and PK of HBI-8000 40 mg BIW in patients with relapsed or refractory PTCL (R/R PTCL). HBI-8000 will be administered orally approximately 30 minutes after any regular meal. The treatment will be continuous, with 3-4 days between dosing. A cycle is defined as 28 days solely for the purpose to schedule assessments required by the study.

The study will continue till the last active Japanese subject initiates administration of the commercial product of HBI-8000 after the marketing authorization approval for relapsed or refractory PTCL in Japan. If there is no subject who is receiving study treatment at the time of the PTCL approval in Japan, the whole study will be completed at the time of the approval.

In Japan, "Phase 2 study" shall be read as "post-marketing clinical study" and "investigator" shall be read as "post-marketing clinical study investigator" in this protocol after the marketing approval. In addition, other related terms are to be replaced in accordance with Article 56 of the Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product (Japan GCP).

Treatment-related adverse events (AEs) will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. In the event of unacceptable toxicities, study drug will be held until recovery and dosing will be resumed at reduced dose level, following protocol guidelines. An unacceptable toxicity is defined as the following:

- Grade 4 afebrile neutropenia > 7 days despite optimal growth factor support
- Grade ≥ 3 febrile neutropenia or neutropenic infection
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding or Grade ≥ 3 thrombocytopenia requiring a platelet transfusion
- Grade ≥3 nausea, vomiting, diarrhea, or electrolyte imbalances lasting greater than 48 hours despite optimal prophylactic and curative treatment
- Grade ≥3 allergic reaction
- Grade ≥3 other non-hematologic AEs
- Treatment delay >14 days secondary to recovery from study drugs- related AEs

For determination of efficacy, HBI-8000 administration will be continued until disease progression (PD) or unacceptable toxicities are observed despite appropriate dose reduction or treatment interruption. Study drug treatment will be discontinued after the PTCL approval when the commercial product of HBI-8000 is available at the study sites.

Number of patients:	40 patients evaluable for efficacy with approximately 27 from Japan and 13 from Korea. To ensure meeting this target, an estimated 50 to 60 patients would be enrolled in anticipation that some patients may not complete study treatment.
Entry Criteria:	**Inclusion** 1. Histological or cytological diagnosis of the following peripheral T-cell lymphoma (PTCL) subtypes as defined by the WHO classification (2008) may be included: a. PTCL, NOS b. Angioimmunoblastic T-cell lymphoma (AITL) c. Anaplastic large-cell lymphoma (ALCL), ALK^+ d. Anaplastic large-cell lymphoma (ALCL), ALK^- e. Enteropathy-associated T-cell lymphoma (EATL) f. Hepatosplenic T-cell lymphoma g. Subcutaneous panniculitis-like T-cell lymphoma 2. Patients for whom at least 1 measurable lesion is confirmed by the lesion assessment at baseline; An evaluable lesion is defined according to Cheson criteria 2014. 3. Relapsed or refractory disease after receiving ≥1 prior systemic therapy with anti-tumor agent(s) and there is no other standard treatment which can be considered appropriate for patients. Systemic therapy is defined as frontline chemotherapy or immunotherapy administered systemically. 4. Male or female, age 20 years or older 5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 6. Life expectancy of greater than 3 months 7. Meeting the following baseline laboratory criteria for screening: a. Absolute Neutrophil Count >1500/μL independent of growth factor support within 7 days b. Platelets >75,000/μL independent of transfusion within 14 days c. Hemoglobin >8 g/dL independent of transfusion within 14 days d. Serum creatinine < 1.5 × ULN e. Serum aspartate aminotransferase/glutamyl oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/glutamyl pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN

f. Serum Bilirubin ≤ 1.5 × ULN

8. Negative serum pregnancy test for females of childbearing (reproductive) potential. Female patients of child bearing potential must use an effective method of birth control (e.g., hormonal contraceptive, intrauterine device, diaphragm with spermicide or condom with spermicide) during treatment period and 1 month thereafter. Males must use an effective method of birth control (2 barrier methods) during treatment period and 3 months thereafter.
   Note: Female patients will be considered to be women of childbearing potential unless having undergone permanent contraception or postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause because of treatment with anti-malignant tumor agents)
9. Signed informed consent

Exclusion

1. Patients in whom central nervous system lymphoma is recognized during screening (if suspected clinically, imaging study should be performed to confirm)
2. Male patients with QTcF >450 msec at screening, female patients with QTcF >470 msec at screening or patients with congenital long QT syndrome, clinically significant arrhythmia, history of congestive heart failure (New York Heart Association Class III or IV) or acute myocardial infarction within 6 months of starting the study drug
3. Patients with known hypersensitivity to benzamide class of compounds or any of the components of HBI-8000 tablets, and patients with prior exposure of HBI-8000
4. Patients with a history of second malignancy other than disease under study. The exceptions are diseases (excluding diseases listed below) that have been treated with curative intent with no evidence of recurrence in past 5 years. Furthermore, if the second malignancy is one of the following diseases that were treated with curative intent, it is only required that there is no evidence of recurrence in past 2 year.
   a. Basal cell carcinoma of the skin
   b. Squamous cell carcinoma of the skin
   c. Cervical carcinoma in situ
   d. Carcinoma in situ of the breast
   e. An incidental histological finding of prostate carcinoma (TNM stage T1a or T1b)
   f. Early-stage gastric cancer treated with endoscopic mucosal resection or endoscopic submucosal dissection
   g. Thyroid cancer with differentiated histology (e.g. papillary) treated with curative intent
5. Autologous stem cell transplantation within 12 weeks (84 days) of starting the study drug
6. History of allogeneic stem cell transplantation
7. Organ transplantation recipients except for autologous hematopoietic stem cell transplantation
8. Uncontrolled inter-current infection
9. Hepatitis B surface antigen-positive, or hepatitis C virus antibody positive. In case hepatitis B core antibody and/or hepatitis B surface antibody is positive even if hepatitis B surface antigen-negative, a

	hepatitis B virus DNA test (real-time polymerase chain reaction (PCR) measurement) should be performed and if positive, the patient should be excluded from study 10. Any history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) 11. Uncontrolled diabetes mellitus, hypertension, endocrine disorder, bleeding disorder 12. Major surgery or radiation therapy within 28 days of starting the study drug 13. Receiving investigational agents or anti-cancer therapy, within 28 days, nitrosourea or mitomycin C within 42 days of starting the study drug 14. Receiving antibody therapy for PTCL within 12 weeks of starting the study drug 15. Women who are breastfeeding or women who are not willing to stop breastfeeding during study treatment period and for 30 days after the last dose of study drug 16. Potential for non-compliance or at increased risk based on investigator's judgement
Excluded Prior or Concomitant Medications or Therapy:	The following drugs are prohibited. • Drugs known to produce significant QT prolongation and ventricular dysrhythmias (see Section 9.6) Prohibited from signing informed consent through the EoT assessment • Anti-cancer therapy other than study medication Prohibited during the study and within the following time intervals prior to the first dose of study drug. - 4 weeks for anti-cancer chemotherapy - 6 weeks for nitrosourea and mitomycin C - 12 weeks for anti-cancer monoclonal antibody therapy Corticosteroid prescribed for medical conditions other than lymphoma is not considered as an anti-cancer therapy for this study, for example: chronic obstructive pulmonary disease, allergy, topical steroids for rash.
Treatments:	Study drug is to be taken after any regular meal twice weekly, each dose separated by 3-4 days. Treatment will continue until PD in the absence of unacceptable toxicity, whichever is earlier. Study drug treatment will be completed when the commercial product of HBI-8000 is available at the study sites after the PTCL approval.
Efficacy Data:	Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma [Cheson 2014]. To be included in final efficacy analyses, the histopathology diagnosis of disease will be verified by Central Pathology Review, and disease response will be confirmed by Independent Radiology and Independent Overall Efficacy Review.
Safety Data:	All patients who receive at least one dose of HBI-8000 will be evaluable for safety. Adverse event severity (grade) will be defined according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Serial ECGs and clinical laboratory tests will be collected to evaluate safety and potential toxicity. Laboratory and other tests, as appropriate to the clinical situation, may be obtained more frequently than stipulated in the schedules of events. All reported AEs will be collected, evaluated and coded using Medical Dictionary for Regulatory Activities (MedDRA).

Pharmacokinetics data from selected sites:	At sites participating in population PK assessments, blood samples for plasma HBI-8000 measurement will be taken on Day 1 of Cycle 1 at pre-dose, 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 30 min), 7 h (± 30 min), 24 ± 1 h, 48 ± 1 h and 72 ± 1 h. On Day 1 of Cycle 2 (e.g., C2D1) PK samples will be taken at pre-dose and 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), and 4 h (± 15 min). On Day 1 of Cycles 3 to 6, only pre-dose PK samples will be taken.

Statistical Procedures:

Statistical analysis for all safety, efficacy, and PK parameters will be primarily descriptive in nature. Categorical variables will be summarized by frequency distributions (number and percentages of patients), 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. A formal statistical analysis plan will be completed prior to database lock and any study-related analyses.

Disease diagnosis including histological subtypes will be confirmed by central pathology review conducted by independent pathologists.

Efficacy should be analyzed using Full analysis set (FAS) and Per protocol set (PPS).

The FAS is defined as Patients meeting all eligibility criteria and having received at least one dose of study medication, and at least one efficacy assessment of disease with either imaging studies or clinical examination after receiving study medication.

The PPS is defined as Patients meeting all eligibility criteria and having completed Cycle 1 treatment or discontinued study treatment during cycle 1 due to clinical PD. It should be noted that the PPS includes subjects who discontinue within Cycle 1 due to clinical PD without imaging studies to assess disease status.

In addition, Patients who are assessed as Non-PTCL by the central pathology review committee should be excluded from the FAS and PPS for efficacy. The non-PTCL subjects will be included in safety analysis for the study.

The primary efficacy analysis is conducted in the PPS. The Efficacy analysis using the FAS will be also reported.

It is estimated that 40 evaluable patients are adequate to provide efficacy assessment. Assuming a 30% ORR in this population of 40 evaluable patients, the conclusion would be that there is a 95% chance that the ORR in this protocol population would lie between 15.8% and 44.2%. The power for showing the response rate >10% at 5% two-sided alpha in 40 patients is 89%.

All patients who have received any amount of study medication will be considered as evaluable for safety. Safety data will be summarized with descriptive statistics and frequency tables and will include AEs, hematology, coagulation, serum chemistry, urinalysis, vital signs, and ECG data. Laboratory values will be summarized by numerical value and toxicity grade.

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large-cell lymphoma
ALT/SGPT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
ATLL	Adult T-cell leukemia/lymphoma
AUC	Area under the curve
BIW	Twice a week
BUN	Blood urea nitrogen
CCR4	CC chemokine receptor 4
CFDA	China FDA
CI	Confidence interval
CKMB	Creatine kinase MB fraction
C_{max}	Peak plasma drug concentration
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CYP	Cytochrome P450
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
EoT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transpeptidase
GPSP	Good Post-marketing Study Practice
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
HSP	Heat shock protein
IB	Investigator's Brochure
IC	Inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
MB	Muscle band
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Disease progression
PET	Positron Emission Tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PMDA	Pharmaceutical and medical devices agency
PPS	Per protocol set
PR	Partial response
PT	Prothrombin time
PTCL	Peripheral T-cell lymphoma
QTcF	QT interval corrected by heart rate, using Fridericia's Correction Formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SiRNA	Small interfering RNA
SOP	Standard operating procedures
TCL	T-cell lymphoma
TEAE	Treatment-emergent adverse event
TIW	Three times a week
ULN	Upper limit of normal

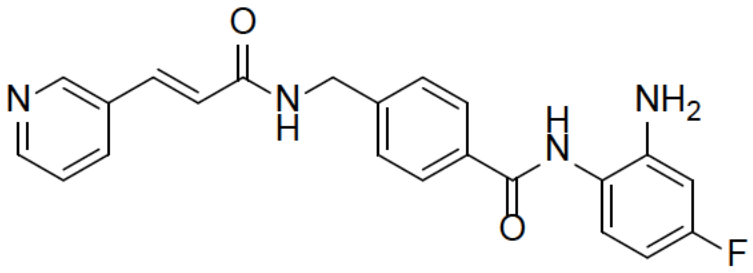
1.0 INTRODUCTION

1.1 Background Information

HBI-8000 (tucidinostat, CS055, chidamide), *N*-(2-Amino-4-fluorophenyl)-4-[*N*-[(*E*)-3-(3-pyridyl)acryloyl]aminomethyl]benzamide is a member of the benzamide class of histone deacetylase inhibitor (HDACi) designed to block primarily the catalytic pocket of Class I histone deacetylase (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 peripheral T-cell lymphoma (PTCL) in December 2014. It is marketed under the trade name Epidaza® in China. HUYABIO International, LLC (HUYABIO) has licensed worldwide rights (excluding China) of this compound. HBI-8000 was approved by Ministry of Health, Labour and Welfare (MHLW) for relapsed or refractory Adult T-cell Leukemia/Lymphoma (ATLL) in Japan on June 23, 2021. The development programs in solid tumors and hematologic malignancies are underway. The terms HBI-8000, tucidinostat and chidamide (CS055) are used interchangeably throughout this document.

The molecular and structural formulas for HBI-8000 are shown below (Figure 1).

Figure 1: Molecular and structural formulas for HBI-8000



HBI-8000 ($C_{22}H_{19}FN_4O_2$; molecular weight, 390.42)

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 for further information on HBI-8000 [IB 2020].

1.2 Histone Deacetylase 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 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, Peart, and Johnstone 2006; Minucci and Pelicci

2006; Glaser et al. 2007; Rasheed, Johnstone, and Prince 2007; Rasheed et al 2008; Haberland, Montgomery, and Olson 2009].

The activity of Class I HDACs (HDAC isoenzymes 1, 2, 3, and 8) is elevated in acute myelogenous leukemia, acute promyelocytic leukemia, non-Hodgkin's lymphoma (NHL), as well as prostate, gastric, colorectal, breast, and cervical cancers [Bolden, Peart, and Johnstone 2006; Nakagawa et al. 2007; Fritzsche et al. 2008; Weichert et al. 2008a; Weichert et al. 2008b]. Small interfering RNA (siRNA)-mediated inhibition of HDAC 1 or 3 resulted in anti-proliferative effects, and HDAC2 inhibition using siRNA sensitized tumor cells to apoptosis [Haberland, Montgomery, and Olson 2009].

Class IIb HDACs (HDAC isoenzymes 6 and 10) preferentially target non-histone proteins, such as α-tubulin and heat shock protein (HSP) 90. Heat shock protein 90 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 receptor. 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-alpha 1-acid glycoprotein and the anti-tumor proteasome inhibitor bortezomib further support these proposed mechanisms [Glaser, et al. 2004, Bali et al. 2005, Rodriguez-Gonzalez et al. 2008, Schemies, Sippl, and, Jung 2009, Park 2008].

Several HDAC inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of T-cell lymphoma (TCL), including vorinostat (ZOLINZA®, Merck & Co. Inc., October 2006) for the treatment of cutaneous manifestations in patients 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 PTCL, and belinostat (BELEODAC®, Spectrum Pharmaceuticals, Inc., July 2014) received accelerated approval from FDA for the treatment of patients with relapsed or refractory PTCL. Panobinostat (FARYDAK®, Novartis Corporation, February 2015) was approved in combination with bortezomib and dexamethasone for the treatment of patients 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 non-small cell lung cancer 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, Modesitt et al 2008, Vansteenkiste et al 2008, Luu 2009].

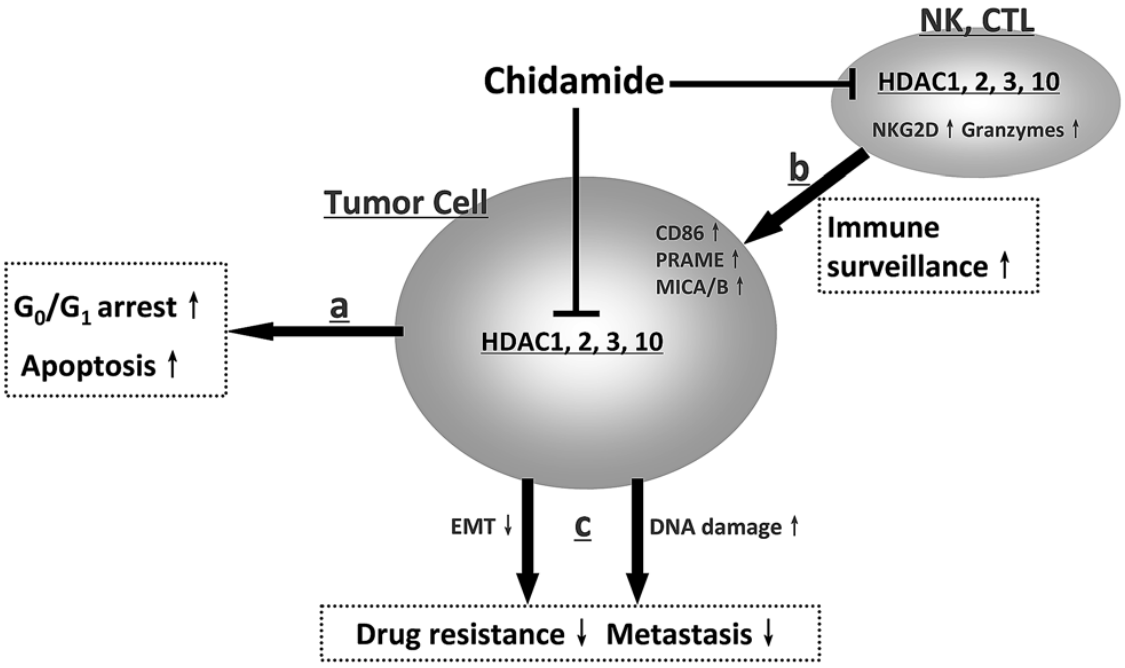
1.3 Rationale for the Use of HBI-8000 for the Treatment of Cancer

HBI-8000 inhibits several cancer-associated Class I (HDAC 1, 2, 3) and one Class IIb HDAC (isoenzymes 10) 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_{50s}) in the single-digit micromolar range. HBI-8000 is non-toxic to non-transformed cells ($IC_{50s} \geq 100$ 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 pharmacokinetics (PK) and toxicology studies in rats and dogs as well as results from a Phase 1 study conducted to date [Shenzhen Chipscreen Study Report 2008] suggest that HBI-8000 has favorable PK and safety profiles.

Emerging data suggest that there are three major mechanisms underlying the anti-cancer activities of HDACi: preferential induction of growth arrest and apoptosis in blood and lymphoid-derived tumor cells, enhancement of both NK-mediated and CD8+ Cytotoxic T lymphocyte -mediated antigen-specific anti-tumor immunity, and partial reversal of epithelial mesenchymal transition and drug resistance of tumor cells as described in Fig. 2. However, the activation of natural killer (NK)- and antigen-specific Cytotoxic T lymphocyte -mediated cellular anti-tumor immunity appears only to be associated with the benzamide type of sel4ctive HDACi such as HBI-8000 (Figure 2).

Figure 2: Proposed manifold anti-tumor mechanisms of chidamide (HBI-8000)



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

It has been theorized 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 could affect immune cell 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 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 increase tumor cell ligands promoting NK cell-mediated tumor cell lysis, and NKG2D expression on NK cells involved in tumor cell lysis, thereby promoting tumor immunocyte interactions involved in immune surveillance. For example, in a pancreatic cancer model, exposure to valproic acid, an inhibitor of HDAC classes 1 and 2 (but not 6 and 10), upregulates NKG2D ligands and major histocompatibility complex class I-related chains A and B (MICA and MICB) in pancreatic cancer cells, thereby increasing susceptibility of tumor cells to NK cell-mediated cell lysis in vitro [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 MIC expression in tumor cells and NKG2D in primary human NK cells [Zhu et al 2015].

1.4 Nonclinical Studies

HBI-8000 is metabolized, in part, by the cytochrome P450 (CYP) 3A4 pathway, and it inhibits CYP3A4 and CYP2C8. The estimated IC_{50}'s of HBI-8000 for CYP inhibition in pooled human liver microsomes were 12.7 μM (CYP2C8) and 1.47 μM (CYP3A4). Other CYP isoenzymes were not significantly inhibited by HBI-8000. Peak plasma concentrations for HBI-8000 in the planned clinical studies are expected to be well below the IC_{50} for inhibition of CYP3A4 and CYP2C8, suggesting low potential for significant inhibition of the metabolism of CYP3A4 or CYP2C8 substrates.

The findings in toxicology studies conducted in the U.S. and China were consistent. At dosing levels just above the 'no observed adverse effect level', the findings across several species were gastrointestinal disturbances, loss of appetite, diarrhea, and myeloid and lymphoid suppression. At higher exposure, these effects increased, and oligospermia and mucosal hemorrhage in the gastrointestinal tract were also observed. Sporadic signs of focal myocardial inflammation and necrosis were seen in some studies, as were occasional prolonged QT intervals in one dog study. All of these cardiac changes were found only at high exposures, were reversible, were inconsistent across studies, and may have been related to the poor metabolic condition of animals receiving such high doses of HBI-8000. Overall, the main

target tissue toxicities of HBI-8000 in rats and dogs are in bone marrow, lymphoid tissue, and the gastrointestinal tract.

Further information on non-clinical studies conducted with HBI-8000/chidamide may be found in the Investigator's Brochure [IB 2020]. For the following discussion, the names HBI-8000 and chidamide are used interchangeably, although chidamide will be used to describe data generated by Chipscreen.

1.5 Clinical Pharmacology

1.5.1 Absorption

The single-dose PK of chidamide was evaluated in 33 patients with TCL. After a single oral administration of 30 mg of chidamide after any regular meal, the average time to peak plasma drug concentration was approximately 4 hours, average peak plasma drug concentration (C_{max}) 60 ng/ml, average area under curve (AUC_{0-t}) 660 ng×h/mL and the average endpoint elimination half-life 17 hours.

The multi-dose PK parameters of chidamide were evaluated in 19 TCL patients administered with multiple doses of chidamide. Compared to that of single dose patients, the AUC_0-t value increased 1.8 folds after the 8th dose, and the differences were statistically significant ($p<0.01$). The correlation between drug exposure and the efficacy and/or safety of chidamide remains to be established.

The effect of dose on PK was evaluated in 21 patients with advanced stage solid tumor or lymphoma. A single dose of 25, 32.5 or 50 mg chidamide tablet was administered, the AUC_0-t 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.

The bioavailability of chidamide appeared to be higher when taken with food. The effect of food on PK was studied in seven patients with TCL. When 30 mg chidamide was ingested 30 minutes after any regular meal, the mean plasma drug exposure was 2.3-fold of that when the same dose was administered in fasting state.

It was observed in the clinical trials that administration of drug after any regular meal could alleviate gastrointestinal irritation caused by the drug in some patients. It is thus recommended to take the medication at least 30 minutes after any regular meal.

In clinical studies conducted in China, it was noted that some clinical features were associated with drug exposure. The time to C_{max} shortened and C_{max} increased with increasing age; average drug exposure (unit AUC_{last}) for male patients was about 80% of that for females at the same dosage. However, its correlation with the efficacy and safety remained unknown.

In a Phase 1 trial conducted in the U.S. (Study HBI-8000-101), HBI-8000 was administered three times a week (TIW) continuously, significant inter-patient variability was observed. There was suggestion of some drug accumulation between Day 1 and Day 19. On Day 19, AUC ranged from 1.3 to 2.2-fold of Day 1 and C_{max} ranged from 0.9 to 3.1-fold of Day 1. Due

to significant variability across doses among 2-3 patients in each dose group, no definitive conclusion could be made. However, no gender difference was observed in this trial.

In a Phase 1 trial conducted in Japan (Study HBI-8000-201), HBI-8000 was administered two times a week continuously.

1.5.2 Distribution

The apparent volume of distribution 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.

1.5.3 Metabolism and Excretion

Nuclear magnetic resonance and liquid chromatography-tandem mass spectrometry were used to investigate the biological conversion and material balance in 4 patients with TCL. 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 clinical pharmacological studies with HBI-8000/chidamide may be found in the Investigator's Brochure [IB 2020].

1.6 Clinical Studies

To date, more than 800 patients have been dosed with HBI-8000/chidamide in clinical trials. Over 26,000 patients have been prescribed chidamide (Epidaza) in China since marketing approval was granted in December 2014.

Clinical trials with HBI-8000 have shown that HBI-8000 is generally well tolerated in patients with advanced solid tumors or relapsed or refractory lymphoma at doses up to 32.5 mg TIW and 50 mg BIW administered continuously with or without intermittent breaks (total weekly doses of approximately 100 mg in Phase 1 trials). The Phase 2 registration study in PTCL conducted in China demonstrated significant efficacy, with the best response rate of 28% (22/79) and a good safety profile. A subgroup analysis of the various histological subtypes revealed that the ORR was as high as 44 to 50% [Shi 2013, Shi 2015]. Based on these data, the CFDA granted conditional approval on December 23, 2014 for the use of chidamide (HBI-8000) for the treatment of relapsed or refractory PTCL.

In Japan, pharmaceutical and medical devices agency (PMDA) was consulted in 2013 to obtain advice for the clinical development of HBI-8000 for relapsed or refractory PTCL and ATLL in Japan. For a Phase 2 dose selection, a Phase 1 study (HBI-8000-201) in patients with relapsed or refractory Non-Hodgkins Lymphoma (NHL) including PTCL and ATLL was

initiated in Japan in April, 2014 and has completed. In addition, Phase 2 study in relapsed or refractory ATLL was initiated in 2016 and has completed. HUYBIO received approval from MLHW for relapsed or refractory ATLL in June 2021. The Phase 2 study in PTCL is this protocol.

1.7 Rationale for Investigation in Relapsed and Refractory Peripheral T-Cell Lymphoma (PTCL)

Peripheral T-Cell Lymphoma (PTCL) s a group of usually aggressive and relatively treatment-resistant peripheral NHLs that develop from mature T cells (TCL). Peripheral T-Cell Lymphomas are sub-classified into various subtypes, each of which are typically considered to be separate diseases based on their distinct clinical, morphologic, immunophenotypic and genetic features [Jaffe 2009]. The 3 most common subtypes of PTCL, not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL), account for approximately 70% of all PTCLs, although there are geographical (North America, Europe and Asia) differences in the prevalence of the different subtypes, with ATLL and NK/T-cell lymphoma being more common in Asia **[**Vose, Armitage, Weisenburger 2008**].**

The frontline therapy for PTCL has been multi-agent chemotherapy. Once disease has relapsed or if disease fails to respond to frontline therapy, treatment options are limited. In Japan, mogamulizumab, a humanized monoclonal antibody directed against chemokine (C-C motif) receptor 4 (CCR4), has been available for the treatment of relapsed or refractory CCR4+ ATLL since 2012 and has been approved by PMDA for PTCL and CTCL based on a Phase 2 clinical trial in 2014. CCR4 is over-expressed on various malignant T cells, including ATLL, PTCL and CTCL cells. Approximately 50% of PTCL patients are CCR4+, hence eligible to receive mogamulizumab.

Clinical trials of mogamulizumab have shown that not all patients would respond to treatment. In fact, the response rate from the Phase 2 trial in Japan was 34% with a median progression free survival (PFS) of 3 months [Ogura et al 2014]. In Phase 1/2 trials conducted in the U.S., the overall response rate (ORR) was 37%, while in the EU, the ORR was only 11% with PFS of 2.1 months [Zinzani et al 2014]. The low ORR (11 to 37%) suggests that about two thirds of mogamulizumab-treated CCR4+ PTCL patients would still require other treatments. Also, clinically significant adverse drug reactions have been observed with mogamulizumab, in particular, Stevens-Johnson Syndrome. Thus, treatment with better efficacy and safety is still needed. The planned study HBI-8000-203 will be conducted to evaluate the efficacy and safety of HBI-8000 in relapsed and refractory PTCL to address an unmet medical need.

1.8 Dose Selection and Risk Assessment

A Phase 1 dose finding study of HBI-8000 was conducted in Japan in NHL patients. Based on the clinical experience from China (Section 1.6) where the CFDA approved dose of chidamide (Epidaza) is 30 mg BIW, the starting dose of this study was 30 mg. Data to date have shown that both 30 mg and 40 mg dose levels were well tolerated. The Grade 3 and 4

toxicities observed at 40 mg in 2 out of 6 patients were transient, and asymptomatic. The grade 4 neutropenia was asymptomatic resolved promptly with administration of granulocyte colony stimulating factor. The Grade 3 alanine aminotransferase (ALT) elevation was also asymptomatic resolved with dosing interruption. On the other hand, strong signals of efficacy were observed at 40 mg as evidenced by none of the seven patients showing disease progression (PD)and five achieving partial response. Upon review of risk and benefit in totality, the 40 mg BIW schedule was selected as the starting dose for the Phase 2.

In clinical studies, treatment with HBI-8000 has been associated with myelosuppression, including thrombocytopenia, neutropenia and/or leukopenia and anemia or decreased hemoglobin. Other adverse drug reactions reported in previous clinical trials include nausea, diarrhea, fatigue/lethargy, abdominal pain, vomiting, peripheral edema, pyrexia/fever, anorexia, dizziness, decreased appetite and transaminase increase. Recommendations for the management of dose modifications are presented in Sections 2.6.8 and 2.6.9.

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2.0 STUDY OBJECTIVE(S)

2.1 Primary Objective

- To determine the efficacy of HBI-8000 administered BIW continuously

2.2 Secondary Objective

- To evaluate the safety and tolerability of HBI-8000 administered BIW continuously

2.3 Criteria for Evaluation

Efficacy Endpoints:

Disease response will be assessed based on evaluation at baseline and postdose evaluations of nodal and extranodal lesions by imaging studies every 8 weeks. Evaluation of nodal lesions and extranodal lesions will be performed according to the revised criteria for response assessment in lymphoma [Cheson 2014] (see Section 9.4).

Primary:

- Objective response rate [ORR; Complete Response (CR) + Partial Response(PR)]

Secondary:

- ORR by disease subtype (see Section 2.5.1)
- Median duration of PFS
- Median duration of response (DOR)

Exploratory:

- Median duration of overall survival (OS)
- Pharmacokinetics (for selected sites)

Safety Endpoints:

Safety and tolerability of HBI-8000 will be measured by the number of patients with adverse events (AEs) and severity of AEs as defined by Common Terminology Criteria for Adverse Events (CTCAE) v.4.03. Adverse events reported by the patients 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.

Population Pharmacokinetic Characterization Study (applicable to participating sites and consented patients):

Population PK will be conducted at selected sites in Japan. At these sites, only patients that consent to this PK study will participate. To obtain comparable PK database from Japan and Korea and to assess regional difference, if any, PK characterization will be required for all patients enrolled in Korea. PK sampling will be performed as detailed in Table 5 of Appendix A.

2.4 Summary of Study Design

This is a Phase 2b, open-label, non-randomized, single arm study to evaluate the efficacy, safety, and PK of HBI-8000 in patients with relapsed or refractory PTCL. Study patients will ingest HBI-8000 approximately 30 minutes after any regular meal BIW. There will be 3 to 4 days between dosing. A treatment cycle is defined as 28 consecutive days. HBI-8000 administration will be continued until PD or the occurrence of unacceptable toxicities despite optimal supportive care.

The study will continue till the last active Japanese subject initiates administration of the commercial product of HBI-8000 after the marketing authorization approval for relapsed or refractory PTCL in Japan. If there is no subject who is receiving study treatment at the time of the PTCL approval in Japan, the whole study will be completed at the time of the approval.

In Japan, "Phase 2 study" shall be read as "post-marketing clinical study" and "investigator" shall be read as "post-marketing clinical study investigator" in this protocol after the marketing approval. In addition, other related terms are to be replaced in accordance with Article 56 of the Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product (Japan GCP).

Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma. [Cheson et al 2014] (see Section 9.4).

2.4.1 Safety Determination and Criteria for Dose Modification or Interruption

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade the severity of toxicities. Abnormalities of laboratory tests (investigation) must be evaluated for clinical significance. Study treatment may be held, and dose may be reduced in the event of unacceptable toxicities. (see Section 2.6.8 for Guidelines.)

2.5 Selection of Study Population

2.5.1 Inclusion Criteria

Patients may be entered in the study only if they meet **all** of the following criteria:

1. Histological or cytological diagnosis of the following PTCL subtypes as defined by the WHO classification (2008) may be included:
    a. PTCL, NOS
    b. Angioimmunoblastic T-cell lymphoma (AITL)
    c. Anaplastic large-cell lymphoma (ALCL), ALK^+
    d. Anaplastic large-cell lymphoma (ALCL), ALK^-
    e. Enteropathy-associated T-cell lymphoma (EATL)
    f. Hepatosplenic T-cell lymphoma
    g. Subcutaneous panniculitis-like T-cell lymphoma

2. Patients for whom at least 1 measurable lesion is confirmed by the lesion assessment at baseline; an evaluable lesion is defined according to Cheson Criteria 2014.
3. Relapsed or refractory disease after receiving ≥1 prior systemic therapy with antitumor agent(s) and there is no other standard treatment which can be considered appropriate for patients. Systemic therapy is defined as frontline chemotherapy or immunotherapy administered systemically.
4. Male or female, aged 20 years or older
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2
6. Life expectancy of greater than 3 months
7. Meeting the following baseline laboratory criteria for screening:
    a. Absolute Neutrophil Count >1500/μL independent of growth factor support within 7 days
    b. Platelets >75,000/μL independent of transfusion within 14 days
    c. Hemoglobin >8 g/dL independent of transfusion within 14 days
    d. Serum creatinine < 1.5 × upper limit of normal (ULN)
    e. Serum aspartate aminotransferase/glutamyl oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/glutamyl pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN
    f. Serum Bilirubin ≤ 1.5 × ULN
8. Negative serum pregnancy test for females of childbearing (reproductive) potential. Female patients of child bearing potential must use an effective method of birth control (e.g., hormonal contraceptive, intrauterine device, diaphragm with spermicide or condom with spermicide) during treatment period and 1 month thereafter. Males must use an effective method of birth control (2 barrier methods) during treatment period and 3 months thereafter.

    Note: Female patients will be considered to be women of childbearing potential unless having undergone permanent contraception or postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause because of treatment with anti-malignant tumor agents)
9. Signed informed consent

2.5.2 Exclusion Criteria

Patients who meet **any** of the following criteria are **not** to be enrolled:

1. Patients in whom central nervous system lymphoma is recognized during screening (if suspected clinically, imaging study should be performed to confirm)
2. Male patients with QTcF >450 msec at screening, female patients with QTcF >470 msec at screening, or patients with congenital long QT syndrome, clinically significant arrhythmia, history of congestive heart failure (New York Heart Association Class III or IV) or acute myocardial infarction within 6 months of starting the study drug
3. Patients with known hypersensitivity to benzamide class of compounds or any of the components of HBI-8000 tablets, and patients with prior exposure of HBI-8000

4. Patients with a history of second malignancy other than disease under study. The exceptions are diseases (excluding diseases listed below) that have been treated with curative intent with no evidence of recurrence in past 5 years. Furthermore, if the second malignancy is one of the following diseases that were treated with curative intent, it is only required that there is no evidence of recurrence in past 2 years:
    a. Basal cell carcinoma of the skin
    b. Squamous cell carcinoma of the skin
    c. Cervical carcinoma in situ
    d. Carcinoma in situ of the breast
    e. An incidental histological finding of prostate carcinoma (TNM stage T1a or T1b)
    f. Early-stage gastric cancer treated with endoscopic mucosal resection or endoscopic submucosal dissection
    g. Thyroid cancer with differentiated histology (e.g. papillary) treated with curative intent
5. Autologous stem cell transplantation within 12 weeks (84 days) of starting the study drug
6. History of allogeneic stem cell transplantation
7. Organ transplantation recipients except autologous hematopoietic stem cell transplantation
8. Uncontrolled inter-current infection
9. Hepatitis B surface antigen-positive, or hepatitis C virus antibody positive. In case hepatitis B core antibody and/or hepatitis B surface antibody is positive even if hepatitis B surface antigen-negative, a hepatitis B virus DNA test (real-time polymerase chain reaction measurement) should be performed and if positive, the patient should be excluded from study
10. Any history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome
11. Uncontrolled diabetes mellitus, hypertension, endocrine disorder, bleeding disorder
12. Major surgery or radiation therapy within 28 days of starting the study drug
13. Receiving investigational agents or anti-cancer therapy within 28 days, nitrosourea or mitomycin C within 42 days, of starting the study drug
14. Receiving antibody therapy for PTCL within 12 weeks of starting the study drug
15. Women who are breastfeeding or women who are not willing to stop breastfeeding during study treatment period and for 30 days after the last dose of study drug
16. Potential for non-compliance or at increased risk based on investigator's judgement

2.6 Study Procedures Overview

Patients may be treated in this study as long as they receive clinical benefit (stable disease or a response) in the absence of unacceptable toxicity. Disease progression would be determined by investigators based on local radiology findings and clinical judgement. No independent radiology review is required prior to designation of PD and treatment discontinuation. Independent Radiology Review and Independent Overall Efficacy Review will be performed for final efficacy analyses at the completion of this study.

To ensure patient safety, a data safety monitoring board (DSMB) will convene to review the cumulative safety profiles of study patients at following milestones: first 6 patients completing at least 1 cycle, 12, 18, 30 patients have been treated for at least 1 cycle and at end of treatment Phase of the study. Based on the observed safety, dose and regimen of ongoing treatment may be modified as needed. For all patients, weekly safety laboratory tests will be obtained during the first 28 days and closely monitored for safety signals, especially for neutropenia and transaminase elevation.

It is estimated that each patient will be on study for up to 42 months after enrollment. Assuming that 24 months are needed to meet accrual target, the study period would be of 66 months to allow efficacy and safety determination. After study drug is discontinued, patients will be followed as described in Sections 2.6.4 and 2.6.5.

Patients will be screened by the study site investigator prior to entry into the study. Patients will receive a detailed explanation of the study design, and the potential risk/benefit of treatment will be disclosed to patients prior to the screening process. Only eligible and consenting patients will be enrolled into the study. Local histopathology report could be used to consent patient. Central pathology review will be completed before efficacy analysis. The investigator will maintain a pre-screening log to record all patients prior to screening.

Similarly, local radiology reports on disease status will guide investigator's decision on study treatment, including discontinuation. At end of the study, tumor response of each patient will be reviewed by independent radiologists and oncologists in a blinded fashion to obtain best response, dates of response and progression. The data from independent and local assessment will be analyzed in parallel in final study report.

The Schedule of Events is presented in Table 4 of Appendix A (Section 9.1). The timing of PK sampling is provided in Table 5 of Appendix A.

2.6.1 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 patients 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 patients meet all eligibility criteria. An Eligibility Screening Form (ESF) documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed and kept at the study site.

Screening assessments include medical history and concomitant medications, documentation of PTCL diagnosis in accordance with the WHO revised classification (WHO 2008) and treatment history. To consent a patient to allow screening procedure, local histology diagnosis for PTCL is acceptable. Unstained tumor pathology slides will be sent to pathology central laboratory and stained at the central laboratory. The images will be captured from the slides for central pathology review that is to be completed before efficacy analysis. For patients who do not have enough tumor tissue archived, a new biopsy will be requested. However, insufficient tumor tissue in archive or inability to perform new biopsy for any reason does not

exclude patients from entering this study. Reasonable efforts should be made to support central pathology review.

Screening assessments will be performed within 28 days prior to Cycle 1 Day 1 (C1D1). A pretreatment bone marrow test (aspiration or biopsy) would be required. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to C1D1 may be used (and do not need to be repeated for screening unless they do not meet the criteria defined in the protocol). Similarly, tumor assessment tests <2 weeks outside the 28-day window in the absence of clinical evidence of PD, the results may be accepted.

Women of childbearing potential must agree to practice effective contraceptive measures after signing informed consent. A negative serum pregnancy test will be obtained during screening.

2.6.2 Baseline Assessments on Cycle 1 Day1 (C1D1)

Baseline assessments include a complete physical examination, vital signs, ECOG performance status, weight, concomitant medications, laboratory tests (hematology, chemistry, coagulation and urinalysis), and safety ECG. Women of childbearing potential must have a negative pregnancy status confirmed by serum test before dosing. If Serum pregnancy test result cannot be obtained on the same day before dosing, urine pregnancy test should be conducted additionally and the result should be confirmed before dosing (see Section 9.1). Some of the pre-dose assessments except vital signs and ECG may be performed 1 day before C1D1 to accommodate scheduling requirements in the hospital.

2.6.3 Treatment Phase

All assessments must be performed as per the Schedule of Events (see Section 9.1. Assessments scheduled on the day of study treatment should be performed prior to taking study drug, unless otherwise noted in the schedule of assessments.

Assessment of tumor response will be scheduled by end of the eighth week, then every 8 weeks (± 1 week) from C1D1. However, if a patient develops clinical signs and symptoms of PD, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed. For the patients with skin lesions, decision on treatment discontinuation should be based on computed tomography (CT) or positron emission tomography (PET-CT) assessment, not Modified Severity Weighted Assessment Tool (mSWAT) scores. In other words, if imaging studies showing SD or PR while mSWAT score increases, treatment will continue.

2.6.4 End of Treatment Safety Follow-up Visit

All patients receiving at least one dose of HBI-8000 and discontinuing treatment for any reason except death will be assessed 30 (± 3) days after the last dosing of study drug, before the initiation of new cancer treatment or before the initiation of administration of commercial product of HBI-8000, whichever is earlier. Any patient for whom study treatment has been discontinued should complete study procedures listed in the EoT visit. At EoT safety visit, evaluations will include physical examination, vital signs, body weight, ECOG performance

status, hematology, blood chemistry, urinalysis, pregnancy test (if applicable), ECG, and assessment of any ongoing adverse events. If a patient discontinues study treatment before PD is recorded, and if the last tumor assessment was >30 days earlier from the EoT visit, tumor assessment should be performed at EoT. In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn or by completion of the whole study. If subjects cannot visit at site for this examination due to COVID-19 situation, investigators can skip the examination, and the assessment is to be performed approximately every 6 months ± 2 weeks. In this case, the investigator should document that fact in the medical record.

Patients 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 patient receives other anti-cancer therapy.

2.6.5 Survival Follow-up

Follow-up for survival (and tumor status in patients in whom PD has not yet been observed) should occur at approximately 3-month intervals after the EoT visit. Survival status may be conducted every 3 months ± 2 weeks by telephone contact or e-mail until death or end of study, defined as timing that the last Japanese subject initiates administration of the commercial product of HBI-8000. If there is no subject who is receiving study treatment at the time of the PTCL approval in Japan, the whole study will be completed at the time of the approval. The first subsequent anticancer therapy during this survival follow up period should be recorded with regimen and start date in the appropriate Electronic Case Report Form (eCRF).

2.6.6 Patient Withdrawal

Patients 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 authority to determine whether a patient should be discontinued from the study. Study treatment may be discontinued and the patient withdrawn from the study under the following circumstances:

- Unacceptable toxicity (AE)
- Progression of the disease under study, except for isolated progression in skin lesion
- Decision by the investigator to permanently discontinue study drug administration
- Intercurrent illness that would, in the judgment of the investigator, affect clinical assessments, patient safety, or follow-up significantly
- Significant protocol deviations that jeopardize the usefulness of the data
- Repeated patient noncompliance
- Patient is beginning another anti-cancer treatment protocol
- Patient becomes pregnant
- Patient requests to withdraw informed consent
- Study termination by the sponsor

All patients who withdraw from study treatment must complete an EoT visit, to be performed 30 ± 3 days after the last dosing of the study drug (see Section 9.1), before the initiation of new cancer treatment or before the initiation of administration of commercial product of HBI-8000, whichever is earlier. A patient may withdraw consent for treatment but still allow follow-up, in which case he/she should be followed for safety, survival, and disease status. If a patient has withdrawn consent to study participation entirely, no subsequent follow-up will be performed.

Patients who are lost to follow up or withdraw consent for study participation prior to receiving HBI-8000 or who withdraw before completing Cycle 1 for reasons unrelated to drug AEs or PD will be replaced.

2.6.7 Discontinuation of the Study

The whole study will be discontinued in any of the following cases:

- Sponsor decides to discontinue development of the compound or the study
- In the event of sponsor or regulatory authorities obtain safety information which does not allow continuation of the study

2.6.8 Management and Dosage Modifications for Unacceptable Hematologic and Non-Hematologic Adverse Events

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 will be used to grade the severity of toxicities. An unacceptable toxicity is defined as the following treatment-related AEs:

- Grade 4 afebrile neutropenia >7 days despite optimal growth factor support
- Grade ≥3 febrile neutropenia or neutropenic infection
- Grade ≥3 thrombocytopenia with clinically significant bleeding or Grade ≥3 thrombocytopenia requiring a platelet transfusion
- Grade ≥3 nausea, vomiting, diarrhea, or electrolyte imbalances lasting greater than 48 hours despite optimal prophylactic and curative treatment
- Grade ≥3 allergic reaction
- Grade ≥3 other non-hematologic AEs
- Treatment delay >14 days secondary to recovery from study drugs- related AEs

Table 1 summarizes the guidelines for dosage adjustment in the event of unacceptable AEs. Two dose reductions are allowed (from 40 mg to 30mg, or from 30 mg to 20 mg). If unacceptable AEs recur despite 2 dose reductions, the study treatment will be permanently discontinued and post-treatment follow-up ensues. However, if the patients are having clinical benefit, further treatment may be considered after discussion with the sponsor. In the event of AE, such as hematological AE-uncomplicated, necessitating two treatment interruptions, dose will be reduced when treatment resumes. However, if strongly needed for patient safety, dose can be reduced according to the investigator judgement, even if unacceptable hematological AE-uncomplicated is occurred once.

Table 1: HBI-8000 Tablet Dosage Adjustment Guidelines

AE Category	AE Description	Dosage interruption with/without Reduction
Hematological Adverse Events--Uncomplicated	• Neutropenia Grade 3 or 4 upon observation	Hold dose, Initiate G-CSF, once resolved to ≤1 within 2 weeks, resume at same dose
	• Thrombocytopenia Grade 3 or 4 upon observation	Hold dose, once resolved to ≤1 within 2 weeks, resume at same dose. If recovery takes >2 weeks, discontinue study drug.
Hematological Adverse Events--Complicated	• Grade 4 afebrile neutropenia >7 days despite optimal growth factor support • Grade ≥ 3 febrile neutropenia or neutropenic infection • Grade ≥3 thrombocytopenia with clinically significant bleeding or Grade ≥3 thrombocytopenia requiring a platelet transfusion	Hold doses, once resolved to ≤1 within 2 weeks, resume at reduced dose (from 40 mg to 30 mg, or from 30 mg to 20 mg); If recovery takes >2 weeks, discontinue study drug.
Non-Hematological Adverse Events (excluding laboratory values without clinical significance)	Grade 3	Hold doses, once resolved to ≤1 within 2 weeks, resume at reduced dose (from 40 mg to 30 mg, or from 30 mg to 20 mg) with appropriate prophylaxis as applicable. If recovery takes >2 weeks, discontinue study drug.
	Grade 4	Discontinue study drug

AE: Adverse Event; G-CSF: granulocyte colony stimulating factor

G-CSF is recommended to be prescribed when uncomplicated grade 3 or 4 neutropenia is observed. Patient management should follow institution guidelines and be recorded in eCRFs. Laboratory tests should be obtained at least once a week to monitor recovery.

2.6.9 Management and Dosage Modifications for Non-Hematologic Adverse Events

In the event of Grade 3 non-hematologic AEs (excluding isolated abnormality of laboratory values not associated with clinical significance), study medication should be held. Appropriate treatment should be initiated. Patients will be closely monitored for recovery and managed following the Dose Adjustment Guideline. If the AEs recur despite two dose reductions as applicable, study treatment should be discontinued. Study treatment should be terminated if Grade 4 non-hematologic adverse events occur, following the Dose Adjustment Guideline.

2.7 Study Drug Administration

During this trial, patients will receive 40 mg HBI-8000 administered approximately 30 minutes after any regular meal as four 10 mg tablets BIW continuously. The dosing interval would be 3 to 4 days for a total of 80 mg over 7 days. At each visit when study medication is dispensed, the study site staff will contact the Interactive Web Response System (IWRS) before dispensing.

2.8 Packaging, Labelling and Storage

HBI-8000 10 mg tablets are packaged in high density polyethylene bottles closed with an induction seal and a child-resistant cap and contain a desiccant pack, and a cotton coil. Each bottle contains 26 tablets. Study drug labels will contain information to meet the applicable regulatory requirements. In case of discontinuation of treatment for any reason unused portion of the drug should be returned to hospital pharmacy.

Drug product will be stored at 2 to 8 ° C at hospital pharmacy until dispensing. After dispensing to patients, the drug will be transported to home in a cooler to maintain refrigerated condition. Once at home, the drug will be kept refrigerated until administration and out of reach of children all the time. The study drug shall be read as post-marketing clinical study drug in this protocol after the PTCL approval.

2.9 Patient Registration and Subject Number Assignment

Based on medical history, potentially eligible patients will be identified. After obtaining informed consent, the screening procedures will be performed and a 5-digit subject number will be assigned. The first 3 digits are the site number (provided by the sponsor to study sites). The last 2 digits are a sequential number within a study site. If a patient is assigned a subject number and later found unable to begin HBI-8000 administration, the patient will be replaced. A new subject number will be assigned to the replacement patient.

2.10 Concomitant Treatments

All concomitant medications, regardless of whether they are prohibited or not, received after signing informed consent must be recorded on the eCRF. Complete information on all concurrent medications (generic name of drugs, reason for use, dosage and duration of dosing, etc.) should be documented in the original records and in the eCRF.

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

2.10.1 Prohibited Medications and Therapy

The following drugs are prohibited.

- Drugs known to produce significant QT prolongation and ventricular dysrhythmias (see Section 9.6)

Prohibited from signing informed consent through the EoT assessment

- Anti-cancer therapy other than study medication

Prohibited during the study and within the following time intervals prior to the first dose of study drug.

- 4 weeks for anti-cancer chemotherapy
- 6 weeks for nitrosourea and mitomycin C
- 12 weeks for anti-cancer monoclonal antibody therapy

Corticosteroid prescribed for medical conditions other than lymphoma is not considered as an anti-cancer therapy for this study, for example: chronic obstructive pulmonary disease for allergy, topical steroids for rash.

Please note that patient use of any prohibited medication is considered a protocol violation. In the event of prohibited medication use, investigator should consult study medical monitor to define an appropriate course of action if needed.

2.10.2 Cautioned Medications

Because the anti-emetic drug Zofran (ondansetron) is well known to prolong QTc, it is prohibited on 2 occasions, Cycle 1 Day 1 and Cycle 2 Day 1 when QTc test is scheduled. Starting 24 hours before the QTc test until the QTc test is completed on the next day, patient must not take Zofran over a 2-day period. Although anti-emetics are rarely needed for HBI-8000, if anti-emetics must be used for other medical reason, alternative drug(s) should be used. If a 5-HT3 antagonist must be used to manage severe emesis refractory to other medications, dosing should be postponed until resolution of underlying medical condition.

In case it is medically necessary to co-administer drugs that could interfere with CYP3A4 activity, investigators should monitor for toxicities and follow the study drug dose modifications for toxicity per study protocol. Also, St. John's wort should be used with caution.

2.10.3 Permitted Medications

Use of supportive care for AEs is permitted. These treatments may include anti-emetics, antipyretics, antidiarrheal, anti-allergy agents, rash reliever, antihypertensive drugs, analgesics, antibiotics, hematopoietic growth factors and transfusion with blood products.

Sulfamethoxazole Trimethoprim use is permitted. However, when its side effects are observed, alternative antibiotics prophylaxis should be considered.

2.11 Dietary Restrictions

Due to potential food-drug interactions for many commonly used medications, grapefruit, grapefruit juice, Seville oranges, and any products that contain Seville oranges or grapefruit should be avoided when possible.

2.12 Treatment Compliance

The prescribed dosage, intervals between doses, and mode of administration, e.g., after meals, intact tablet (not crushed) may not be changed without direction by the investigators. They must be recorded in the eCRFs.

The patient will be provided with a drug log to record date and time of administration, time of meal prior to administration, AEs, and missed doses. To verify compliance, the patient will be instructed to bring the drug log and study drug bottles (including any empties) to appointments scheduled for Day1 of each cycle starting with Cycle 2 for reconciliation.

At each visit when study medication is dispensed previously dispensed study drug count will be confirmed by the investigator, or authorized designee, and compliance assessed prior to dispensing new study medication.

Patients exhibiting poor compliance as assessed by tablet counts and not following dosing schedules should be counseled on the importance of good compliance to the study dosing regimen. Noncompliance to drug amount is defined as taking <75% or >125% of study medication during a cycle. Noncompliance to dosing interval is defined as more than 2 occurrences of <3 days between doses during a cycle, for example, 1 or 2 days between doses #3 and #4 instead of 3 or 4 days according to a BIW schedule. If in the opinion of investigator a patient is unable to follow instruction, study treatment should be discontinued.

2.13 Study Medication Accountability

A clinical supplies shipment/receipt verification form will be enclosed with each study drug shipment. The site pharmacist who receives the shipment should complete this form and clinical research associate should collect a copy of the form at each pharmacy visit. If instead of the shipment/receipt verification form, a packing list is enclosed with the shipment, acknowledgment of the study drug receipt should be done through the IWRS system by the site pharmacist or authorized designee.

The investigator, or authorized 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 supplies should be accounted for at the termination of the study, and a written explanation provided for any discrepancies. All unused study medication supplies and

packaging materials are to be inventoried and returned to the local depot by the investigator, or authorized designee. The investigator, or authorized designee, is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by the sponsor or delegate(s).

3.0 STUDY ASSESSMENTS

3.1 Efficacy

3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is to establish the ORR, defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period, evaluated by using the revised criteria for response assessment in lymphoma [Cheson 2014] (see Section 9.4).

Tumor assessments will be performed by imaging modalities. CT, magnetic resonance imaging, or PET scanning may be used to evaluate lesions in the neck, chest, abdomen, and pelvis; and as a baseline evaluation for patients who may have brain metastases. The PET-CT is encouraged to be performed from baseline. However, when CT is the routine method to monitor patients according to hospital standard of care, PET-CT is not required. Evaluation of nodal lesion and extranodal lesion will be performed according to the revised criteria for response assessment in lymphoma [Cheson 2014] (see Section 9.4). Skin lesions are non-target lesions. Their response will be assessed according to mSWAT, and contribute to overall response determination.

Tumor response based on imaging studies will be confirmed with central review by independent radiologists at end of study prior to final efficacy analysis. The dates of PR, CR and PD will be assessed as applicable. Initial review will be performed by one independent radiologist. If the results differ from those reported by the investigators based on local radiology findings, a second independent radiologist will be asked to adjudicate by way of assigning the final disease response to the determination made by either the investigators or independent radiologist. The overall efficacy review will be done by independent oncologist for final efficacy analysis.

3.1.2 Secondary Efficacy Endpoints

The secondary efficacy measures are:

- ORR by disease subtype
- Median duration of PFS defined as the time from the first dose of study medication to objective tumor progression or death.
- Median DOR defined as the time from the first observation of tumor response to PD.

3.1.3 Exploratory Endpoints

- Median duration of overall survival
- Pharmacokinetics

3.2 Safety

3.2.1 Definitions

3.2.1.1 *Adverse Events*

An AE is any unfavorable and unintended sign (including an 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 patient'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 from signing the informed consent.

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

3.2.1.2 *Serious Adverse Event*

A serious adverse event (SAE) is any untoward medical occurrence resulting in the following:

- Death
- Is life-threatening (defined as an event in which the patient was at 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-patient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization, but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical or surgical] to prevent one of the other serious outcomes listed in the definition above). 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 SAE form and sent to the sponsor in an expedited manner.

All pregnancies, regardless of outcome, must be reported to the sponsor on a pregnancy form, not an SAE form.

NOTE:

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

- A visit to the emergency room or other hospital department lasting <24 hours, that does not result in admission (unless considered "important medical event" or event that is "life-threatening")
- Elective surgery planned prior to signing consent
- 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 purpose other than remedying ill health state and was planned prior to signing consent. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)
- Admission for Progressive Disease (PD)

3.2.2 Period of Observation

All AEs (including SAEs) regardless of the relationship to study drug or study procedure will be collected from obtaining informed consent to the EoT assessment. At EoT, AEs Grade ≥2 considered to be at least possibly related to the study drug must be followed up after the EoT assessment until the events have recovered to Grade ≤1, returned to the baseline level, are judged by the investigator to be stabilized, or to be given a reason that further follow up will not be required (see Section 2.6.4). However, if the patient begins to receive new cancer therapy or withdraws consent to study participation, no further follow-up will be conducted. The outcome of the events which do not resolved by that time will be recorded as "ongoing" on the eCRF.

3.2.3 Preexisting Conditions

A preexisting condition will not be reported as an AE unless the condition worsens by at least one CTCAE grade during the study. However, the pre-existing condition must be recorded in the screening eCRF as a pre-existing condition, and all concomitant medication administered for the condition must be recorded as concomitant medication in the eCRF following guidelines for other concomitant medication.

3.2.4 Documentation and Reporting of Adverse Events by Investigator

Any signs and symptoms that occur after obtaining the informed consent will be described as AEs and graded according to the CTCAE in the AE section of the eCRF.

Abnormal laboratory values will be recorded on the laboratory section of the eCRF and not in the AE section. Abnormal laboratory results leading to a clinical diagnosis will be reported with a clinical term by the investigator and 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 SAE form. Relationship (reasonable causal relationship) to drug treatment and countermeasures taken will be noted on the eCRF. Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy.

Disease progression should not be recorded as an AE. Diagnostic and therapeutic non-invasive 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 be reported.

3.2.5 Assessment of Causal Relationship to Study Drug

The relationship of an AE to the study medication is graded 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 patient's clinical state or other factors

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

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

Unrelated:
- Definitely not associated with the study drug administered

"Definite", "Probable" and "Possible" events are regarded as AEs that cannot be denied a causal relationship to the study drug, that will be handled as "related to the study drug" for reporting purposes, and "Unlikely" and "Unrelated" events are regarded as AEs that can be denied a causal relationship to the study drug, that will be handled as "not related to study drug" for reporting purposes.

3.2.6 Intensity of Adverse Events

The intensity of adverse changes in clinical signs or symptoms will be graded according to the CTCAE. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator using the following categories:

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 refer 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 refer to bathing, dressing and undressing, feeding self, 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

3.2.7 Events Requiring Immediate Reporting

3.2.7.1 *Serious Adverse Events*

Adverse events classified as "serious" must be reported in timely fashion to comply with regulatory requirements. All suspected unexpected serious adverse reactions associated with the use of HBI-8000 will be reported to the regulatory authorities in accordance with the Guideline for Industry International Council for Harmonisation (ICH) E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

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 must be made within 24 hours, irrespective of the extent of available AE information. In case the eCRF cannot be used by investigator to generate the SAE/Pregnancy form, a paper SAE/Pregnancy form will be used and will be faxed to [redacted]. Once the eCRF limitation is resolved, the investigator should enter all the information from the paper report into the eCRF as soon as possible.

[redacted]

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the sponsor 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. All SAEs occurring in this study requiring expedited regulatory reporting will be evaluated, summarized, and reported to investigators. These SAEs must also be submitted in writing by investigators to the institutional review board (IRB).

3.2.7.2 *Pregnancy*

If a patient becomes pregnant during treatment or within 1 month following the last dose of the study drug, administration (if still ongoing) must be discontinued and the sponsor is notified within 24 hours of investigator awareness of the pregnancy. For the purposes of this study, pregnancy of any patient will be considered an AE but not, in itself, an SAE, and should be reported to the sponsor on a pregnancy form rather than an SAE form. However, if pregnancy leads to an SAE for example, a spontaneous abortion or miscarriage resulting in medical hospitalization, an SAE form should be completed. Every attempt must be made to follow the pregnancy to resolution, which includes birth or termination of the pregnancy. If the information is available, the resolution must be reported to the sponsor on a pregnancy form. If possible, births should be followed by the investigator for 8 weeks for observation of any congenital abnormalities, and any such abnormalities should be reported within 24 hours of investigator awareness of the observation to the sponsor.

Pregnancy of a male patient's partner will not be considered an AE, and the male patient should not be withdrawn from the study. If a male patient's partner becomes pregnant during the specified time period (from first dose until 3 months after the last dose), the investigator will inform the sponsor within 24 hours of investigator awareness of the pregnancy, as well as the IRB, as appropriate, and will provide appropriate medical follow-up, if agreed to by the partner.

3.2.7.3 *Overdose*

Overdose is defined as administration to the patient of a dose of test article that exceeds by more than 40 mg/dose or 80 mg/week.

Any overdose of HBI-8000 should be reported via an 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 SAE form and specify the intended amount, as well as the actual amount, of drug administered.

3.2.8 Follow-Up of Adverse Events

Patients should be asked to specifically describe any signs, symptoms, or AEs (regardless of relationship to therapy) they may notice prior to the start of the study or thereafter. At a minimum, patients should be asked to report AEs at each visit to the study site. Conditions that the patient experienced prior to informed consent should be recorded in the medical history section of the eCRF.

Follow up of an "overdose" should include continued monitoring of all protocol-specific laboratory results, including chemistry and hematology, using the protocol-specified time points for laboratory tests, with the exception that an additional full series of chemistry, hematology, and coagulation tests, a full physical examination, vital signs, and ECG should be conducted within 24 hours of investigator awareness of that the patient received an "overdose". Following this additional ad hoc re-evaluation, the investigator should use his or her medical judgment in deciding whether additional supplemental medical treatment is needed to treat adverse medical consequences of the overdose. Also after the ad hoc re-evaluation, the investigator should use his or her medical judgment in deciding whether additional supplemental monitoring is needed to track resolution of any AEs or other abnormal findings to the point of resolution to a CTCAE Grade 1 AE.

3.2.9 Clinical Laboratory Evaluations

Clinical laboratory tests, fasting or post meal, will be reviewed for results of potential clinical significance at all time points throughout the study. The abnormality will be graded under Investigation category of CTCAE version 4.03 independent of clinical significance. The investigator will evaluate any change in laboratory values.

Hematology testing will include the following parameters: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count, coagulation, including prothrombin time, activated partial thromboplastin time (aPTT), and International Normalized Ratio.

Serum chemistry testing will include the following parameters: blood urea nitrogen, creatinine, AST, ALT, gamma-glutamyl transpeptidase, total bilirubin (including direct fraction if total bilirubin is abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, random blood glucose, lactate dehydrogenase (LDH), creatine kinase MB fraction.

Urinalysis (glucose, protein, occult blood test) will be performed by dipstick method, and in the event of abnormal dipstick results, additional test may be required.

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

- Subject number
- Time and date of dose administration
- Time and date of patient's most recent ingestion of food prior to dose administration

3.2.10 Vital Signs, Physical Findings and Other Safety Assessments

Vital signs measurements will include pulse rate and systolic and diastolic blood pressure in a seated position of at least 5 minutes.

Physical examinations will be performed. A skin assessment will be conducted per the standard procedure of the site. For skin lesions, photograph with an adjacent ruler to indicate size will be obtained, if needed.

ECG are to be 12-lead. Vital signs measurements should be performed prior to the ECG.

To assess QTc intervals, 12-lead ECGs in triplicate will be obtained at 3.5 ± 0.5 hours after taking study medications on C1D1 and C2D1. The patient should be in seating position for 5 minutes before the 1st ECG is obtained, followed by 2nd and 3rd ECGs with 5 ± 2 minutes between ECG measurements.

3.3 Pharmacokinetics

Pharmacokinetic sampling for population PK will be performed as detailed in Table 4: of Appendix A.

Blood samples (2 mL) will be drawn into evacuated tubes containing dipotassium ethylene diaminetetra acetic acid. Each sample will be inverted several times and then placed immediately into an ice bath. Within 30 minutes of sampling, tubes must be centrifuged at 1,000 × g at 4ºC for 5 minutes. Plasma fractions will then be transferred in 200 µL aliquots into 2 cryogenic vials. The cryogenic vials will be labeled as A or B, plus the unique subject number, collection time, and date before being frozen. Samples will be placed and stored at -70ºC within 30 minutes of transfer to the cryogenic vial. The original sample for PK analysis (A) and the duplicate sample (B) will be stored at -70°C. For each patient participating PK study, PK (A) samples from Cycles 1 and 2 could be shipped together after Cycle 2 Day 1. The site could also ship all samples (Cycles 1 to 6) from each individual patients in one shipment. Samples from several patients could be batched together for shipment as well. The shipment for back-up samples (B) would be handled similarly. PK samples (A) and samples (B) will be shipped to [redacted].

Details of sample collection, handling, storage, and transport methodology will be provided to the investigator in the laboratory manual.

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

- Subject number
- Time and date of dose administration (as well as time and date of previous dose administration for PK samples collected from Cycle 2 onwards)
- Time and date of each blood sample collected for pharmacokinetic analysis
- Time and date of patient's most recent ingestion of food prior to dose administration

3.4 Blood Volume

The total blood volume for each patient to be collected at screening is approximately 20 mL. Blood volume collected for safety tests on Days 1, 8, 15, and 22 of Cycle 1 will be approximately 30 mL. Assuming each patients would receive up to 6 Cycles of treatment, subsequent cycles will have blood collections for safety tests on Days 1 and 15 of Cycle 2 then Day 1 of Cycles 3 to 6. The total blood collection volume for Cycles 2 to 6 will be approximately 58.5 mL. The total blood collection volume for EoT will be approximately 6 mL for safety tests. For patients participating in PK study, blood volume for PK would be 30 mL for Cycle 1, 15 mL for Cycle 2 and 2 mL pre-dose on Day 1 of Cycles 3 to 6. For patients receiving treatment Cycle 7 and beyond, there will be no PK blood sample except for 10.5 mL blood for safety tests. The assumptions are listed in Table 2 and Table 3.

Table 2: Screening Cycle 1

	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Hematology	5	2	10
Serum chemistry	5	4	20
Coagulation	3	4.5	13.5
Hepatitis B virus tests	1	2	2
Hepatitis C virus tests	1	4	4
Total (excluding PK)			49.5
Pharmacokinetics	10	3[a]	30
Total (PK participating patients)			79.5

PK: pharmacokinetic

[a] The sample volume of 3 mL includes 1 mL of blood needed for flushing the catheter tubing prior to a sample collection.

Table 3: Cycles 2 to 6

	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Hematology	6	2	12
Serum chemistry	6	4	24
Coagulation	5	4.5	22.5
Total (excluding PK)			58.5
Pharmacokinetics cycle 2 day 1	5	3[a]	15
Pharmacokinetics cycles 3-6 day 1	4	2	8
Total (PK participating patients)			81.5

PK: pharmacokinetic

[a] The sample volume of 3 mL includes 1 mL of blood needed for flushing the catheter tubing prior to a sample collection.

3.5 Independent Review

3.5.1 Data Safety Monitoring Board

A DSMB has been established to monitor the safety observed during the conduct of this study. For all patients, weekly safety laboratory tests should be obtained during the first 28 days and closely monitored for safety signals, especially the neutropenia and transaminase elevation. DSMB consists of 3 oncologists who are experienced in treating patients with PTCL and are not associated with this study. They are assisted by one DSMB statistician.

DSMB convenes at planned intervals based on patient accrual (see Section 2.6). Upon reviewing cumulative safety data from the study and taking into consideration of state-of-the-art medical practice, they will advise sponsor for treatment modification including dose adjustment, AE management, and continuation of treatment.

3.5.2 Independent Radiology Review

To ensure consistent radiology method is applied to assess disease response across the entire study, designated radiologists will review sequential imaging studies of individual patients. They will assign response outcome including best response, dates of initial response and progression when applicable, based on Cheson Critieria. They will be blinded to the local radiology findings. Should discrepancy between assessments by independent radiologist and site occur, a 2nd independent radiologist will adjudicate by selecting assessment from either site or 1st independent radiologist for final analysis.

3.5.3 Central Pathology Review

To ensure consistent diagnosis of PTCL subtypes, a panel of pathologists with appropriate expertise will review pathology slides from archival tumor specimens or biopsy as applicable. The techniques, such as immunohistochemistry staining, will be according to standard of practice using agreed methodology, no later than the end of study.

3.5.4 Independent Overall Efficacy Review

To ensure consistent overall efficacy review method is applied to assess disease response across the entire study, designated independent oncologists will review sequential clinical data of individual patients including radiological assessment provided by the independent radiological review. They will assign response outcome including best response, dates of initial response and progression when applicable, based on Cheson Criteria 2014.

4.0 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 Standard Operating Procedures (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:

- Clinical laboratory parameters
- Study site initiation visit
- Early site visits post-enrollment
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the clinical study report (CSR)

In addition, sponsor may conduct periodic audits of the study processes, including, but not limited to study site, site visits, clinical laboratories, vendors, clinical database, and final CSR. 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.

4.1 Monitoring

The sponsor has engaged the services of a contract research organization, [redacted], to perform all monitoring functions within this clinical study. [redacted]' monitors will work in accordance with [redacted]' 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 site, 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 patients 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 site. 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 site while patients 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 number
- Patient consent obtained
- Patient eligibility criteria (inclusion and exclusion criteria)
- Efficacy variables
- Medical record of AE

4.2 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 [redacted].

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

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the patient's visit.

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 centre 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 patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria and all records covering the patient's participation in the study. They include laboratory notes, electrocardiogram (ECG) results, memoranda, pharmacy dispensing records, patient 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 patient 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 patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. 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 UserID 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 Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 Concomitant medications will be coded using WHO-DDE. Concomitant diseases/medical history will be coded using MedDRA.

4.3 Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the Principal investigator (Japan: Head of study site) 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, pertinent 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.

4.4 Quality Assurance Audit

Study sites, the study database and study documentation may be subjected to Quality Assurance audit during the course of the study by the sponsor or delegate(s) on behalf of the sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

4.5 Site Audits

The principal investigator 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.

5.0 STATISTICS

5.1 General Statistical Considerations

Protocol HBI-8000-203 is an open-label, Phase 2b pivotal study evaluating HBI-8000 for regulatory approval in Japan and South Korea for the indication of relapsed or refractory PTCL. The main analysis will be conducted for the purpose of regulatory submission of this product. The data cut-off (DCO) for the main analysis is set at the time when the last patient completes at least one post-efficacy assessment. The eCRF data by the DCO needs to be cleaned to have no unresolved queries. All independent reviews (including the Central Pathology Review, the independent radiological review, the Independent Overall Efficacy Review and review by the Data Safety Monitoring Board) by the DCO need to be completed before the main analysis. The data after the main analysis will be provided at the end of the study as a supportive material.

Statistical analysis for all safety, efficacy, and PK parameters will be primarily descriptive in nature. Categorical variables will be summarized by frequency distributions (number and percentages of patients), 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 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.

5.2 Determination of Sample Size

For efficacy determination, 40 patients evaluable for efficacy per protocol criteria are required. To ensure meeting this target, an estimated 50 to 60 patients would be enrolled in anticipation that some patients may not complete study treatment. Enrolled patients will be treated with the starting dose of 40 mg BIW to provide an assessment of tumor response as well as additional safety data. It is planned that 34 to 40 patients (27 evaluable patients) will be coming from Japan and 16 to 20 patients (13 evaluable patients) will be coming from Korea.

The target best ORR for this study is 30%, on the basis of the ORR results that were obtained in study TG0902CDM. The 95% confidence interval (CI) for an ORR of 30% at a sample size of N=40 is expected to be between 15.8% and 44.2%.

The power for showing the response rate >10% at 5% two-sided alpha in 40 patients is 89%.

The 95% confidence interval for an objective response rate (assumed to be 30%) at various sample sizes are shown below:

ORR (expected)	N	95% CI
30%	25	(12.0 – 48.0)
	30	(13.6 – 46.4)
	35	(14.8 – 45.2)
	40	(15.8 – 44.2)

5.3 Treatment Assignment and Blinding

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

5.4 Replacement of Patients

Patients 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 or PD will be replaced.

5.5 Populations for Analysis

5.5.1 Safety Population

The safety analyses population will include all patients 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.

5.5.2 Efficacy Population

Efficacy should be analyzed using FAS and PPS.

The FAS is defined as Patients meeting all eligibility criteria and having received at least one dose of study medication, and at least one efficacy assessment of disease with either imaging studies or clinical examination after receiving study medication.

The PPS is defined as Patients meeting all eligibility criteria and having completed Cycle 1 treatment or discontinued study treatment during cycle 1 due to clinical PD. It should be noted that the PPS includes subjects who discontinue within Cycle 1 due to clinical PD without imaging studies to assess disease status.

In addition, Patients who are assessed as Non-PTCL by the central pathology review committee should be excluded from the FAS and PPS for efficacy. The non-PTCL subjects will be included in safety analysis for the study.

The primary efficacy analysis is conducted in the PPS. The Efficacy analysis using the FAS will be also reported.

5.5.3 Pharmacokinetic Population

All patients who have pretreatment baseline and at least 1 blood sample on study providing PK data for HBI-8000.

5.5.4 Patient Disposition

Data tabulations will summarize the following patient numbers:

- Enrolled
- HBI-8000 treatment dose received
- Evaluable for safety and efficacy
- Protocol violations
- Protocol completions
- Withdraw from study due to:
  - Adverse event
  - Physician's recommendation
  - Withdrew consent
  - Lost to Follow-up
  - Other reasons as collected on the eCRF

5.6 Patient Characteristics

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

- Age
- Gender
- Race
- Ethnicity
- ECOG Performance Status
- Prior therapies
- Other baseline characteristics as collected on the eCRF

5.7 Concomitant Medications

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

5.8 Treatment Administration

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.

5.9 Efficacy Analysis

The efficacy endpoints are the following:

Primary Endpoint:

- ORR(CR + PR)

Secondary Endpoint:

- ORR by disease subtype (see Section 2.5.1)
- Median duration of PFS
- Median DOR

Exploratory Endpoint

- Median duration of OS

Response rate endpoints (ORR and ORR by disease subtype) will be summarized by number and percentage of patients meeting the definition of ORR along with the corresponding exact 95% CI. Tumor response as assessed by imaging studies will be adjudicated by independent radiology reviewers. Tumor lesions, such as skin lesion, that cannot be monitored by imaging studies will determined by independent oncology reviewers and contributed to overall disease response assessment. Both investigators reported and independently adjudicated outcomes will be reported. Primary analysis will be based on results from imaging studies and clinical data confirmed by Independent Central Review. Results from investigator assessment will also be reported. In addition, the ORR will be analyzed according to histology subtypes of PTCL. The subtypes reported by Central pathology review for each patient will be used for such analysis.

Time-to event endpoints (PFS, DOR, and OS) for entire study population will be summarized by Kaplan-Meier methods (median, 95% CI, number of events, number censored and Kaplan-Meier figures).

5.10 Safety Analysis

All patients who receive 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 AEs and laboratory abnormalities.

5.10.1 Adverse Events

Adverse events will be classified using the MedDRA classification system version 19.0 or higher. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

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. TEAEs will be summarized by the frequency of patients experiencing TEAEs corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE (version 4.03) 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.

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

5.10.2 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 analyses with CTCAE grades, abnormal laboratory values will be summarized by shift tables displaying numerical values and percentages classified by Baseline grade (e.g., grade prior to dosing on Day 1 of Cycle 1) and maximum grade on treatment. All laboratory data will be presented in listings.

5.10.3 ECGs

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, QTc and QTcF) will be summarized descriptively 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 patients with QT or QTc (QTcF) outlier values (at any post-baseline time point), as defined in ICH E14, will be summarized.

5.10.4 Vital Signs and Physical Findings

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

Physical findings will be presented in data listings.

5.10.5 Interim Analysis

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

5.11 Pharmacokinetic Analysis

In patients participating in PK study, peripheral blood will be sampled at specified time points. Plasma concentration of HBI-8000 will be listed and summarized using descriptive statistics. PK data collected in this study will be combined with PK data collected from other studies and a population PK analysis will be performed. Results of the population PK analysis will be presented in a report separate from the CSR.

6.0 ETHICS

6.1 Institutional Review Board or Independent Ethics Committee

The protocol, ICF and any other written information and/or materials to be provided to the patients and the amendments (as required by local regulations) should be reviewed and approved by the IRB/Independent Ethics Committee (IEC). The sponsor's authorized representative should be provided with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study center(s).

The only circumstance in which an amendment may be initiated prior to the sponsor and IRB/IEC approval is where the change is necessary to ensure the safety of the patients. In that case, the investigator must document the change and notify the sponsor and IRB/IEC in writing immediately after the implementation.

The investigator should submit written summaries of the study status for review by the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the investigator will provide a brief report of the outcome of the study, if required. The sponsor and/or the sponsor's authorized representative will handle the distribution of any of these documents to the national regulatory authorities.

6.2 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.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human patients. 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 patients are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki. In Japan, the study shall be conducted in accordance with Good Post-marketing Study Practice (GPSP) as well as GCP after the PTCL approval.

6.3 Patient Information and Informed Consent

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

The investigator is responsible for ensuring that informed consent is obtained from each patient or the legal guardian 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 patient with a copy of the signed and dated consent form.

Whenever important new information becomes available that may be relevant to the patient's consent, the approved by the IRB/IEC, revised information will be provided to each patient in the trial for signing and dating. The investigator will explain the changes to the previous version.

6.4 Patient 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. Information about study subjects will be kept confidential and managed according to the regulatory requirements.

7.0 STUDY ADMINISTRATION

7.1 Administrative Structure

The administrative structure and study organization is presented in Protocol addendum.

7.2 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. Patient identification codes (patient 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 the sponsor and/or the sponsor's authorized representative. The investigator must contact the sponsor and/or the sponsor's authorized representative prior to disposing of any study records.

The U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of study drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the principal investigator for 15 years after the last marketing application approval in an ICH region or after at least 15 years have elapsed since formal discontinuation of clinical development of the investigational drug.

No records should be disposed of without the written approval of the sponsor and/or the sponsor's authorized representative.

For studies conducted outside the United States under a U.S. IND, the principal investigator must comply with U.S. FDA investigational new drug regulations and with those of the relevant national and local health authorities.

7.3 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 patient enrolled into the study.

The investigator will allow the sponsor, the sponsor's authorized representative(s), and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual patient medical records, as appropriate.

7.4 Investigator Information

7.4.1 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; European Legislation; and Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product [Japan GCP]) and the ethical principles that have their origin in the Declaration of Helsinki, and the applicable regulatory requirements of each region. In Japan, the study shall be conducted in accordance with GPSP as well as GCP after the PTCL approval.

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.

7.4.2 Protocol Signatures

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the sponsor or representative (Appendix G). 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 Good Clinical Practice and applicable regulatory requirements. In Japan, the investigator will conduct the study in accordance with GPSP as well as GCP after the PTCL approval. The study will not be able to start at any site where the investigator has not signed the protocol.

7.4.3 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 site will be set forth in the Clinical Trial Agreement.

7.5 Financing and Insurance

The sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable. The terms of the insurance will be kept in the study files.

8.0 REFERENCES

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9.0 APPENDICES

9.1 Appendix A: HBI-8000-203 Schedule of Events

Table 4: Schedule of Events

	Screening	Cycle 1					Cycle 2			Cycle ≥ 3[a]	EoT[b]	Survival F/U[c]
DAY	**-28 to 0**	**1**		**8±2**	**15±2**	**22±2**	**1±4**		**15±4**	**1±7**		
		Pre-dose[p]	**3.5 hrs**				**Pre-dose**	**3.5 hrs**		**Pre-dose**		
HBI-8000[d]		BIW[e]					BIW[e]			BIW[e]		
Written informed consent	X											
Medical history, diagnosis and treatment history, demographics, height	X											
Physical examination, weight	X	X			X		X		X	X	X	
ECOG Performance Status	X	X					X			X	X	
Vital signs[f]	X	X			X		X		X	X	X	
12 Lead ECG (Safety)	X									X	X	
12 Lead ECG (QTc)		X[g]	X[g]				X[g]	X[g]				
Hematology [h]	X	X		X	X	X	X		X	X	X	
Coagulation[h]	X	X			X		X			X		
Chemistry[i]	X	X		X	X	X	X		X	X	X	
Urinalysis[j]	X	X									X	
Hepatitis B/C virus tests[k]	X											
Serum pregnancy test (if applicable)[l]	X	X									X	
Tumor assessment [m]	X									X[m]	X[m]	X[m]
PK blood samples		X[n]					X[n]			X[o]		
Patient survival; new cancer therapies												X

	Screening	Cycle 1					Cycle 2			Cycle ≥ 3[a]	EoT[b]	Survival F/U[c]
DAY	**-28 to 0**	**1**		**8±2**	**15±2**	**22±2**	**1±4**		**15±4**	**1±7**		
		Pre-dose[p]	**3.5 hrs**				**Pre-dose**	**3.5 hrs**		**Pre-dose**		
Adverse events assessment	X	X		X	X	X	X		X	X	X	
Concomitant medication	X	X		X	X	X	X		X	X	X	

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BIW, twice weekly; BUN, blood urea nitrogen; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EoT, end of treatment; F/U, follow-up; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; LDH, lactate dehydrogenase; mSWAT, Modified Severity-Weighted Assessment Tool; PET-CT, positron emission tomography-computer tomography; PCR, polymerase chain reaction; PK, pharmacokinetic; PT, prothrombin time;

a Cycle/Day designation is based on actual calendar days after the first dose. All visits and assessments may be performed ± 7 days to accommodate unforeseen delays, holidays, or vacations.

b "End of Treatment" visit should be conducted 30 ± 3 days after the last dosing of the study drug, before the initiation of new cancer treatment or before the initiation of administration of commercial product of HBI-8000, whichever is earlier.

c Survival data will be collected every 3 months ± 2 weeks after End of Treatment until death or the end of the study, defined as timing that the last Japanese subject initiates administration of the commercial product of HBI-8000.

d Drug administration BIW for 4 weeks ; On the days of scheduled visits that is the same as the dosing scheduled day, patient should take study drug after receiving confirmation from investigator to continue study treatment.

e Dose adjustments based on hematological and non-hematological criteria.

f Pulse rate, diastolic and systolic blood pressure in seated position of 5 minutes. On days when ECGs are taken, vital signs to be taken shortly prior to ECG recording.

g Pre-dose and post dose at 3.5 ± 0.5 hours in triplicates, 5 ± 2 minutes between 1st and 2nd, 2nd and 3rd ECGs, on Day 1 of Cycles 1 and 2.

h Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count; Coagulation tests (PT, aPTT, and INR).

i BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium and random blood glucose, LDH, CKMB (creatine kinase MB fraction)

j Urinalysis (glucose, protein, occult blood test) will be performed by dipstick method, and in the event of abnormal dipstick results, additional test may be required.

k Hepatitis B surface antigen-positive, or hepatitis C virus antibody positive. In case hepatitis B core antibody and/or hepatitis B surface antibody is positive even if hepatitis B surface antigen negative, a hepatitis B virus DNA test (real-time PCR measurement) should be performed and if positive, the patient should be excluded from study.

l Only for women of childbearing potential, including those who have had a tubal ligation. Confirmatory test at the Cycle 1 Day 1 (C1D1) visit should be done before dosing at the local laboratory. If Serum pregnancy test result cannot be obtained on the same day before dosing, urine pregnancy test should be conducted additionally and the result should be confirmed before dosing. Only at EoT visit, Serum and Urine are both acceptable.

m Complete tumor assessment of all lesions by radiographic or other modality. Baseline bone marrow test (aspiration or biopsy) is required. Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma [Cheson 2014], however, PET-CT is not required but encouraged. Skin lesions, if present, will be assessed by mSWAT and contribute to overall tumor response determination by investigators. Assessment of tumor response will be scheduled by end of the 8th week, then every 8 weeks (± 1 week) from C1D1, However, if a patient develops clinical signs and symptoms of disease progression, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed. If a patient discontinues study treatment before disease progression (PD) is recorded, and if their last tumor assessment was >30 days earlier from EoT visit, tumor assessment should be performed at EoT. In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn or by completion of the whole study. If subjects cannot visit their study site for this examination due to COVID-19 situation, investigators can skip the examination, and the assessment is to be performed approximately every 6 months ± 2 weeks. In this case, the investigator should document that fact in the medical record.

n PK sampling on C1D1 pre-dose and 1 h (± 15 mins), 2h (± 15 mins), 3h (± 15 mins), 4h (± 15 mins), 5h (± 30 mins), and 7h (± 30 mins), then 24 ± 1, 48 ± 1 and 72 ± 1 hours in consenting patients; and C2D1 pre-dose and 1 h (± 15 mins), 2h (± 15 mins), 3h (± 15 mins), and 4h (± 15 mins).

o Day 1 of cycles 3 to 6 pre-dose PK sample only.

p Some of the pre-dose assessments except vital signs and ECG may be performed one day before C1D1 to accommodate scheduling requirements in the hospital.

Table 5: Schedule of Pharmacokinetic Blood Draws

Cycle/Study Day	Measurement Time
Cycle 1 Day 1	Predose 1 hour (± 15 mins) postdose 2 hours (± 15 mins) postdose 3 hours (± 15 mins) postdose 4 hours (± 15 mins) postdose 5 hours (± 30 mins) postdose 7 hours (± 30 mins) postdose
Cycle 1 Day 2	24 ± 1 hours postdose
Cycle 1 Day 3	48 ± 1 hours postdose
Cycle 1 Day 4	72 ± 1 hours postdose
Cycle 2 Day 1	Predose 1 hour (± 15 mins) postdose 2 hours (± 15 mins) postdose 3 hours (± 15 mins) postdose 4 hours (± 15 mins) postdose
Day 1 of Cycles 3 to 6	Predose

9.2 Appendix B: Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
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
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

9.3 Appendix C: New York Heart Association (NYHA) Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Farrell MH et al. JAMA. 2002; 287:890-897

- (1) Raphael C et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007;93(4):476-82
- (2) MeReC Bulletin 2008; 18 (3):1-9.
- (3) National Institute for Health and Clinical Excellence (NICE) 2010. Chronic heart failure. National clinical guideline for diagnosis and management in primary and secondary care

9.4 Appendix D: Method of Efficacy Assessment

Overall response will be assessed according to recommendations for Hodgkin and nonHodgkin lymphoma developed in International Conference on Malignant lymphoma in Lugano, Switzerland, 2011, and published in 2014 (Cheson 2014). Patients will have pretreatment assessment at screening and postdose evaluations on Day 1 of subsequent cycles. Imaging studies such as CT to evaluate nodal and extranodal lesions will performed at end of the 8th weeks, then every 8 weeks (± 1 week) from C1D1. However, if a patient develops clinical signs and symptoms of disease progression, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed. If a patient discontinues study treatment before disease progression (PD) is recorded, and if their last tumor assessment was > 30 days earlier from EoT visit, tumor assessment should be performed at EoT. In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn.

9.4.1 Evaluation at Screening

At screening, physical examination is not considered quantitative assessment of lesion size. Disease lesion(s) will be evaluated by imaging studies (CT or PET-CT), bone marrow test (aspiration or biopsy), and skin evaluation. In case gastrointestinal lesion is suspected, endoscopy and biopsy (as needed) will be performed.
All lesions are categorized into the following:

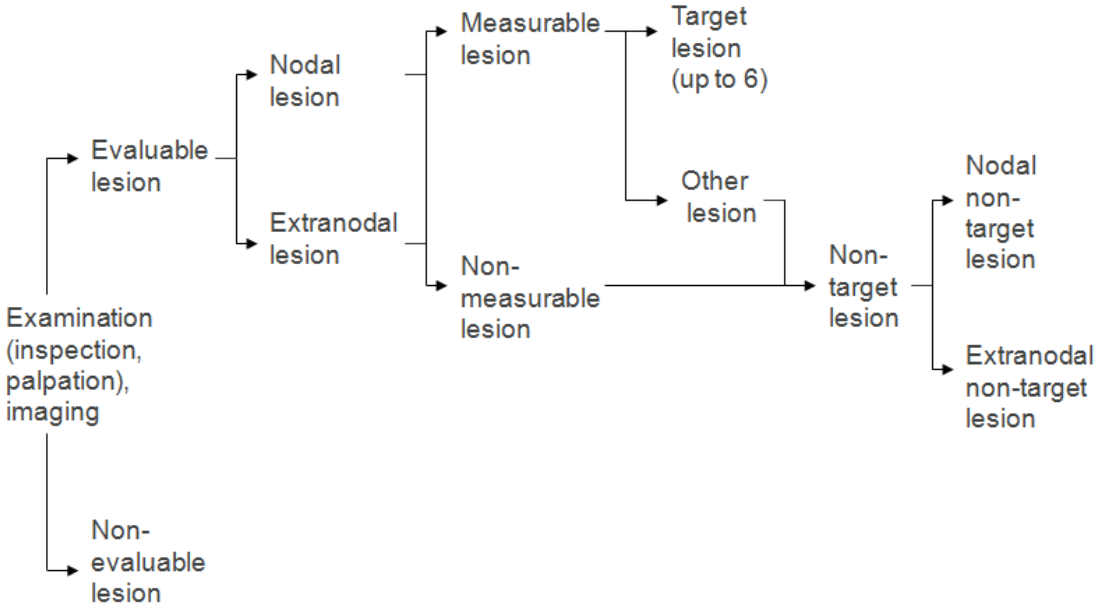
- lesion which can be used for efficacy assessment (hereinafter, evaluable lesion)
- lesion which cannot be used for efficacy assessment (hereinafter, non-evaluable lesion)

In addition, evaluable lesions are categorized into the following:

- measurable lesion
- nonmeasurable lesion

Next, target lesions (up to 6 lesions) are selected from measurable lesions.
Nonmeasurable lesions and other measurable lesions are deemed as non-target lesions.

Figure 3: Selection of Lesions



9.4.2 Imaging

Before the start of study drug administration, evaluation by CT images of neck, chest, abdomen, and pelvis that are taken by a pitch of 5 mm preferable (as for neck image, a pitch of 2.5 to 5 mm will be preferred) will be performed. Same imaging techniques should be used at baseline and on study assessment. PET-CT is encouraged, but not required.

9.4.2.1 *Definition of lesion which can be used for efficacy assessment (evaluable lesion)*

Nodal lesion with the size > 1.5 cm by longest transverse dimension (LDi) on sectional image (e.g, enlarged lymph node) at screening and extranodal lesion which can be followed by imaging are defined as evaluable lesion.

9.4.2.2 *Definition of lesion which cannot be used for efficacy assessment (non-evaluable lesion)*

Non-evaluable lesion is defined as nodal lesion with LDi ≤ 1.5 cm on sectional image of CT at screening and extranodal lesion that cannot be followed by imaging.

9.4.2.3 *Definition of Measurable Lesion (common with nodal and extranodal lesion)*

In evaluable lesions, measurable lesion is defined as the lesion that meets both following criteria:

- The LDi > 1.5 cm on sectional image of CT for nodal lesion; and > 1.0 cm for extranodal lesion
- Definitely measurable by 2 perpendicular dimensions (LDi and its perpendicular dimension) on sectional image of CT

9.4.2.4 *Definition of Non-measurable lesion*

In evaluable lesions, non-measurable lesion is defined as the lesion that meets any of the following criteria:

- Enlarged lymph node: Lesion with the LDi > 1.5 cm on sectional image of CT, but not definitely measurable by 2 dimensions (LDi and its perpendicular dimension)
- Extranodal lesion: All lesions that can be followed by imaging, but do not meet the definition of measurable lesion

9.4.2.5 *Nodes or Extranodal Lesions That Split When Disease Is Responding*

If a confluent nodal mass splits into several discrete nodes, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as a target lesion at baseline).

9.4.2.6 *Nodes or Extranodal Lesions That Become Confluent When Disease Is Progressing*

If a group of target lymph nodes becomes confluent, the PPD of the current confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in the PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and shortest diameter are no longer needed to determine progression.

9.4.3 Selection of Target Lesions

Target lesions are selected from measurable lesions, which can be nodal lesion and extranodal lesion, along with the following criteria:

- Lesions that is suitable to be measured exactly and continuously by the same method.
- Up to 6 lesions in descending order by LDi length on sectional image of CT. If measurable lesions are less than 6, all measurable lesions are selected.
- Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.

The lengths of LDi (cm) and the largest diameter (cm) which is perpendicular to LDi are measured, and their product (PPD) is the cross product of LDi and the PPD for the lesion. The sum of PPD of all target lesions (SPD) will be calculated at screening.

9.4.4 Definition and Selection of Non-target Lesion

Measurable lesions that are not selected as target lesion and non-measurable lesions are defined as non-target lesions.

Non-target lesions are separately evaluated as nodal non-target lesions and extranodal nontarget lesions. If any tumor lesions are found through gastrointestinal endoscopy, the lesion is to be evaluated as extranodal non-target lesion.

9.4.5 Evaluation of Skin Lesion

In case tumor lesion on skin exists, the lesion is considered as non-target. Skin lesion which can be monitored for efficacy should be followed. Investigators can consult dermatologists in sites or clinics if needed.

If it is difficult to determine whether or not skin lesion exist by inspection, biopsy will be performed to diagnose histopathologically.

Skin lesions will be followed according to Severity-Weighted Assessment Tool (Stevens et al 2002): Revised Edition (mSWAT).

9.4.6 Evaluation by Modified Severity-Weighted Assessment Tool (mSWAT) (Olsen et al. 2011)

A total of body surface area (%BSA) of each part is defined in Table 6and Figure 4 (e.g., head 7, neck 2, and anterior trunk 13) in which total body surface area of human is defined as 100.

After %BSA of each type of lesion (patch, plaque, tumor mass, or ulcer) and normal skin is assessed by body parts, percentage of total body surface area (%TBSA) of each type of lesion will be calculated by adding %BSA of total body by type of lesion. In addition, mSWAT score is defined as summation (0 to 400) of product of %TBSA and each summation factor (see the following formula).

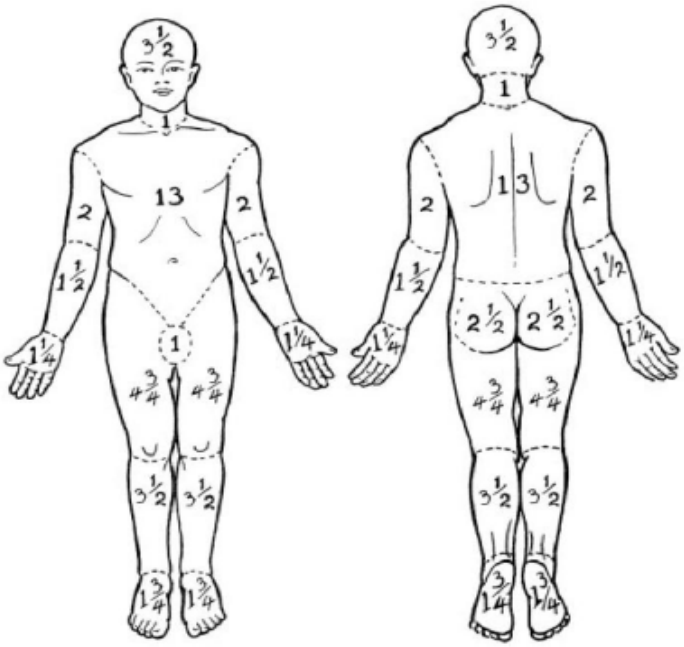
mSWAT score = (%TBSA of patch ×1) + (%TBSA of plaque × 2) + (%TBSA of tumor mass and ulcer × 4)

Table 6: Modified Severity Weighted Assessment Tool (mSWAT)

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque**	Tumor***
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion % BSA				
Weighting factor				
Subtotal lesion BSA X weighting factor				

NOTE. mSWAT score equals summation of each column line.
Abbreviations: BSA, body surface area
*Any size lesion without induration or significant elevation above the sur- rounding uninvolved skin; poikiloderma may be present.
**Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
***Any solid or nodular lesion >1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Figure 4: Percentage BSA of each Part of Human Body



9.4.7 Presence or absence of splenomegaly

Presence or absence of splenomegaly which are considered to be caused by infiltration of lymphocyte is assessed by CT. To be considered positive, the vertical length of spleen must be >13 cm by CT.

9.4.8 Evaluation of infiltration to bone marrow

Infiltration to bone marrow will be evaluated by PET-CT or bone marrow aspiration or biopsy. When bone marrow evaluation is selected, the results will be categorized into the following:

- Positive: Presence of apparent malignant findings including infiltration of abnormal lymphocyte and abnormality in assembly
- Undetermined: Increase of lymphocyte aggregation without infiltration of abnormal lymphocyte or abnormality in assembly
- Negative: Absence or minimal findings of lymphocyte aggregation.

9.4.9 Postdose Evaluation

Imaging studies will be performed by the same method as screening.

9.4.9.1 *Evaluation of target lesion*

Efficacy for target lesion will be assessed by calculating reduction rate (A) and growth rate (B) of the SPD according to the following formula:

$$(A) = \frac{(C) \text{ at screening} - (C) \text{ at evaluation}}{(C) \text{ at screening}} \times 100$$

$$(B) = \frac{(C) \text{ at evaluation} - \text{minimum } (C)^{*1}}{\text{minimum } (C)^{*1}} \times 100$$

*1: minimum (C) value obtained during the study including the screening

(C) = SPD

9.4.9.2 ***Criteria for Response Assessment***

Table 7: Summary of Response Criteria

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to <1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable.	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Lymph nodes and extralymphatic sites	Partial metabolic response Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease	Partial remission (all of the following) ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value

	At end of treatment, these findings indicate residual disease	When no longer visible, 0mm × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease Individual target nodes/nodal masses	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or	Progressive disease requires at least 1 of the following PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ;:50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions < 2 cm 1.0 cm for lesions > 2 cm

		In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Nonnodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson BD, Fisher RI, Barrington SF, et al. (2014) Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 32(27):3059–3067

9.4.9.3 *Evaluation of skin lesion by mSWAT*

Criteria for assessment for tumor shrinkage effect on skin lesion by mSWAT are as following:

- CR: 100% clearance of skin lesion*
- PR: 50 to 99% clearance of skin disease from baseline without new lesion
- SD: < 25% increase to < 50% clearance in skin disease from baseline without appearance of new lesion.
- PD: ≥25% increase in skin disease from baseline or New tumor mass** or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score.

* In case distinguish between residual lesion and normal skin tissue is difficult, CR is determined after confirming disappearance of skin lesion by biopsy.

** tumor mass : at least 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth

9.5 Appendix E: Blood Sample Collection

Caution for use concerning vacuum blood-collection tubes

The test kits provided for the clinical study include vacuum blood-collection tubes. Since reflux may occur due to inappropriate handling of a vacuum blood-collection tube resulting in the contents and/or contaminants in the blood-collection tube to flow into the patient's body, the notifications (Notification No. 1117001 of PFSB, "Voluntary inspection of caution for use and other relevant information concerning vacuum blood-collection tube", dated 17 November 2003 and Notification No. 0104001 of PFSB, "Additional information on the caution for use concerning vacuum blood-collection tubes" dated 04 January 2005 issued by Director of Safety Division) were released to draw your attention to usage of vacuum blood-collection tubes. Please pay attention to the precautions listed below and use the vacuum blood-collection tubes of this study with care.

1. Caution for use of sterile vacuum blood-collection tubes
   - The temperature of the blood-collection tubes prior to blood draw must be equivalent to the room temperature (the inner pressure may change, which could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).
   - Do not move, or release the pressure applied on the arm of the patient before removing the blood-collection needle (moving the position of, or releasing the pressure applied on the arm may cause rapid decrease in the venous blood pressure, which could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).
   - After the blood starts flowing into the collection tube, do not apply force on the tube that could push it into the blood-collection holder (the inner pressure may change, which could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).
   - Do not remove the tourniquet after the completion of blood draw unless otherwise the blood-collection needle is removed first (changes in the pressure due to removal of the tourniquet could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).
   - The holder is for single-patient use only, and should be disposed of after each use (the holder may be contaminated with the blood, which could cause cross infection).
   - Do not draw blood from extracorporeal circuit or central vein (changes in the pressure could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).

2. Instruction for operation or usage
   - The temperature of the blood-collection tubes should be equivalent to the room temperature.
   - The puncture site should be disinfected after the tourniquet is applied.
   - The blood-collection tube should be pushed into the holder straight and completely.
   - The blood-collection tube should be removed from the holder as soon as the blood flow into the tube stops.
   - Consecutive blood draws should be performed with the holder fixed in place and the collection tube replaced.
   - Upon completion of the blood draw, the tourniquet should be kept applied until after the collection tube is removed from the holder.

3. Basic cautions of importance

The blood-collection tube and the patient's arm should point downward at all time during the blood draw.

When using a winged needle for blood draw, ensure that the blood-collection tube does not move up and down.

9.6 Appendix F: Drugs known to produce significant QT prolongation and ventricular dysrhythmias

The following list includes examples of drugs known to produce significant QT prolongation and ventricular dysrhythmias, of which the use is prohibited from signing informed consent through the EoT assessment. This is not an exhaustive list.

If there are any concerns regarding prohibited medications, please consult the sponsor or CRO Medical Monitor.

<Drugs known to produce significant QT prolongation>

alendronate sodium hydrate	amiodarone hydrochloride	apomorphine hydrochloride hydrate
arsenic trioxide	atazanavir sulfate	azithromycin hydrate
bepridil hydrochloride hydrate	cinacalcet hydrochloride	ciprofloxacin
clarithromycin	clofarabine	clomipramine hydrochloride
dasatinib hydrate	delamanid	denosumab
disopyramide	donepezil hydrochloride	droperidol
ebastine	erythromycin	escitalopram oxalate
famotidine	fesoterodine fumarate	fluconazole
fosfluconazole	galantamine hydrobromide	garenoxacin mesilate hydrate
haloperidol	hydroxyzine hydrochloride	hydroxyzine pamoate
ibandronate sodium hydrate	imidafenacin	imipramine hydrochloride
isoflurane	lenvatinib mesilate	levofloxacin hydrate
lomefloxacin hydrochloride	maprotiline hydrochloride	methadone hydrochloride
mianserin hydrochloride	miconazole	minodronic acid hydrate
mirtazapine	moxifloxacin hydrochloride	ofloxacin

panitumumab	pentamidine isetionate	probucol
procainamide hydrochloride	propiverine hydrochloride	prulifloxacin
quinidine sulfate hydrate	roxithromycin	sertraline hydrochloride
sitafloxacin hydrate	solifenacin succinate	sotalol hydrochloride
sulpiride	sultopride	tiapride hydrochloride
trazodone hydrochloride	venlafaxine hydrochloride	voriconazole
chloroquine	chlorpromazine	domperidone
flecainide	propafenone	pimozide

<Drugs known to produce significant ventricular dysrhythmias >

anagrelide hydrochloride hydrate	arsenic trioxide	carperitide
ebastine	furosemide	interferon alfa
miconazole	oxaliplatin	pazopanib hydrochloride
peginterferon alfa	pentamidine isetionate	probucol
ribavirin	sunitinib malate	vandetanib

9.7 Appendix G: Signature of Investigator

PROTOCOL TITLE: A Phase 2b Open-Label Single Arm Study to Evaluate the Efficacy and Safety of Oral HBI-8000 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

PROTOCOL NO: HBI-8000-203

This protocol is a confidential communication of HUYABIO International, LLC. I confirm that I have read this protocol, I understand it, and I will comply with the all the terms and requirements of 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, LLC.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted. Return the signed copy to [redacted]

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 Site: _____

_____

_____

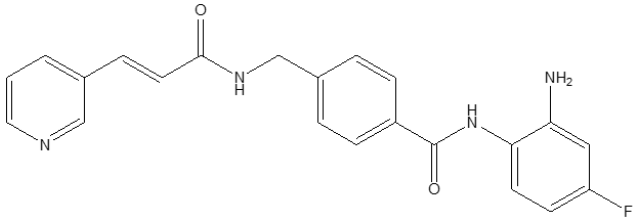
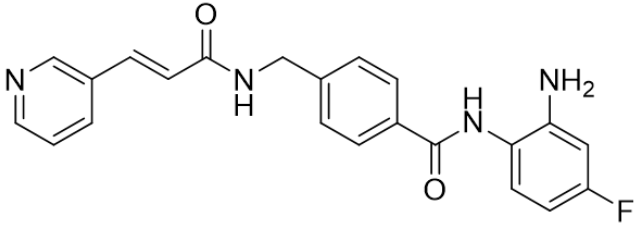
Protocol：HBI-8000-203 version 6.0

Protocol Table of Changes（19 July 2021）

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
Applicable section		HUYA International, LLC	HUYABIO International, LLC	Company name change
Applicable section		IB 2019	IB 2020	Information update
Applicable section			tucidinostat	Addition of general name
Applicable section		ATL	ATLL	Correction
1	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 HUYA Bioscience International, LLC and constitute Confidential Information under the Confidential Disclosure Agreement (CDA) between the parties. The study will be conducted according to the International Council for Harmonisation (ICH)	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 and constitute Confidential Information under the Confidential Disclosure Agreement (CDA) between the parties. The study will be conducted according to the International Council for Harmonisation (ICH) harmonised tripartite guideline E6 (R2): Good Clinical Practice (GCP), including	Confidential description change

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
		harmonized tripartite guideline E6(R2): Good Clinical Practice (GCP), including the archiving of essential documents.	the archiving of essential documents.	
3	Study duration	Approximately 60 months	Approximately 66 months	Study duration extension
3	Planned study period	4Q 2016 (first patient in) to 3Q 2018 (last patient in) 4Q 2021 study completion	4Q 2016 (first patient in) to 3Q 2018 (last patient in) 2Q 2022 study completion	Study duration extension
3	Study Design		The study will continue till the last active Japanese subject initiates administration of the commercial product of HBI-8000 after the marketing authorization approval for relapsed or refractory PTCL in Japan. If there is no subject who is receiving study treatment at the time of the PTCL approval in Japan, the whole study will be completed at the time of the approval. In Japan, "Phase 2 study" shall be read as "post-marketing clinical study" and "investigator" shall be read as "post-marketing clinical study investigator" in this protocol after the marketing approval. In addition, other related terms are to be replaced in accordance with Article 56 of the Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product (Japan GCP).	Change of the study design to complete the study

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
4	Study Design	For determination of efficacy, HBI-8000 administration will be continued until disease progression (PD) or unacceptable toxicities are observed despite appropriate dose reduction or treatment interruption.	For determination of efficacy, HBI-8000 administration will be continued until disease progression (PD) or unacceptable toxicities are observed despite appropriate dose reduction or treatment interruption. Study drug treatment will be discontinued after the PTCL approval when the commercial product of HBI-8000 is available at the study sites.	Change of the study design to complete the study
6	Treatments	Study drug is to be taken after any regular meal twice weekly, each dose separated by 3-4 days. Treatment will continue until PD in the absence of unacceptable toxicity.	Study drug is to be taken after any regular meal twice weekly, each dose separated by 3-4 days. Treatment will continue until PD in the absence of unacceptable toxicity, whichever is earlier. Study drug treatment will be completed when the commercial product of HBI-8000 is available at the study sites after the PTCL approval.	Change of the study design to complete the study
13	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	ATL Adult T-cell lymphoma	ATLL Adult T-cell leukemia/lymphoma	Correction
13	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS		GPSP Good Post-marketing Study Practice	Addition
14	LIST OF ABBREVIATIONS		MHLW Ministry of Health, Labour and Welfare	Addition

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
	AND DEFINITIONS OF TERMS			
15	1.1 Background Information			Replacement
15	1.1 Background Information	molecular weight, 390.41	molecular weight, 390.42	Correction
15	1.1 Background Information		HBI-8000 was approved by Ministry of Health, Labour and Welfare (MHLW) for relapsed or refractory Adult T-cell Leukemia/Lymphoma (ATLL) in Japan on June 23, 2021.	Information update
21	1.6 Clinical Studies	To date, more than 300 patients have been dosed with HBI-8000/chidamide in clinical trials. Over 1000 patients have been prescribed chidamide (Epidaza) in China since marketing approval was granted in December 2014.	To date, more than 800 patients have been dosed with HBI-8000/chidamide in clinical trials. Over 26,000 patients have been prescribed chidamide (Epidaza) in China since marketing approval was granted in December 2014.	Information update
21	1.6 Clinical Studies	Phase 2 clinical trial on going in patients with relapsed or refractory PTCL.	In addition, Phase 2 study in relapsed or refractory ATLL was initiated in 2016 and has completed. HUYBIO received approval from MLHW for relapsed or refractory ATLL in June 2021. The Phase 2 study in PTCL is this protocol.	Information update

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
21	1.8 Dose Selection and Risk Assessment	A Phase 1 dose finding study of HBI-8000 has been conducted in Japan in NHL patients. Based on the clinical experience from China (Section 1.6) where the CFDA approved dose of HBI-8000 is 30 mg BIW	A Phase 1 dose finding study of HBI-8000 was conducted in Japan in NHL patients. Based on the clinical experience from China (Section 1.6) where the CFDA approved dose of chidamide (Epidaza) is 30 mg BIW	
24	2.4 Summary of Study Design		The study will continue till the last active Japanese subject initiates administration of the commercial product of HBI-8000 after the marketing authorization approval for relapsed or refractory PTCL in Japan. If there is no subject who is receiving study treatment at the time of the PTCL approval in Japan, the whole study will be completed at the time of the approval. In Japan, "Phase 2 study" shall be read as "post-marketing clinical study" and "investigator" shall be read as "post-marketing clinical study investigator" in this protocol after the marketing approval. In addition, other related terms are to be replaced in accordance with Article 56 of the Ministerial Ordinance on the Standards for the Implementation of Clinical Studies on Pharmaceutical Product (Japan GCP).	Change of the study design to complete the study
27	2.6 Study Procedures Overview	It is estimated that each patient will be on study for up to 36 months after enrollment. Assuming that 24 months are needed to meet accrual target, the study period would be of 60 months to allow efficacy and safety determination.	It is estimated that each patient will be on study for up to 42 months after enrollment. Assuming that 24 months are needed to meet accrual target, the study period would be of 66 months to allow efficacy and safety determination.	Study duration extension
28	2.6.4 End of	All patients receiving at least one dose of HBI-8000	All patients receiving at least one dose of HBI-8000 and	Change of

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
	Treatment Safety Follow-up Visit	and discontinuing treatment for any reason except death will be assessed 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.	discontinuing treatment for any reason except death will be assessed 30 (± 3) days after the last dosing of study drug, before the initiation of new cancer treatment or before the initiation of administration of commercial product of HBI-8000, whichever is earlier.	the study design to complete the study
29	2.6.4 End of Treatment Safety Follow-up Visit	In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn.	In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn or by completion of the whole study. If subjects cannot visit at site for this examination due to COVID-19 situation, investigators can skip the examination, and the assessment is to be performed approximately every 6 months ± 2 weeks. In this case, the investigator should document that fact in the medical record.	Change of the study design to complete the study and COVID-19
29	2.6.5 Survival Follow-up	Survival status may be conducted every 3 months ± 2 weeks by telephone contact or e-mail until death or end of study, defined as 12 months after the administration of the last dose of the entire study	Survival status may be conducted every 3 months ± 2 weeks by telephone contact or e-mail until death or end of study, defined as timing that the last Japanese subject initiates administration of the commercial product of HBI-8000. If there is no subject who is receiving study treatment at the time of the PTCL approval in Japan, the whole study will be completed at the time of the approval.	Change of the study design to complete the study
30	2.6.6 Patient Withdrawal	All patients who withdraw from study treatment must complete an EoT visit, to be performed 30 ± 3 days	All patients who withdraw from study treatment must complete an EoT visit, to be performed 30 ± 3 days after the	Change of the study

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
		after the last dosing of the study drug (see Section 9.1) or before the initiation of new cancer treatment, whichever is earlier.	last dosing of the study drug (see Section 9.1) ,before the initiation of new cancer treatment or before the initiation of administration of commercial product of HBI-8000, whichever is earlier.	design to complete the study
32	2.8 Packaging, Labelling and Storage		The study drug shall be read as post-marketing clinical study drug in this protocol after the PTCL approval.	Change of the study design to complete the study
56	6.2 Ethical Conduct of the Study		In Japan, the study shall be conducted in accordance with Good Post-marketing Study Practice (GPSP) as well as GCP after the PTCL approval.	Change from study to post-marketing study
59	7.4.1 Investigator Obligations		In Japan, the study shall be conducted in accordance with GPSP as well as GCP after the PTCL approval.	Change from study to post-marketing study
59	7.4.2 Protocol Signatures	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	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 Good Clinical Practice and	Change from study to post-marketing

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
		for Good Clinical Practice and applicable regulatory requirements. The study will not be able to start at any site where the investigator has not signed the protocol.	applicable regulatory requirements. In Japan, the investigator will conduct the study in accordance with GPSP as well as GCP after the PTCL approval. The study will not be able to start at any site where the investigator has not signed the protocol.	study
60		8.0 STUDY DURATION	8.0 REFERENCES	Correction
60	8.0 REFERENCES	IB 2019: Investigator's Brochure for HBI-8000 (CS055, chidamide). HUYA Bioscience International, LLC version 9, 08July2019.	IB 2020: Investigator's Brochure for HBI-8000 (tucidinostat). HUYA Bioscience International, LLC version 10.1, 18November2020.	Information update
64	Table 4: Schedule of Events b	"End of Treatment" visit should be conducted 30 ± 3 days after the last dosing of the study drug, or before the initiation of new cancer treatment, whichever is earlier	"End of Treatment" visit should be conducted 30 ± 3 days after the last dosing of the study drug, before the initiation of new cancer treatment or before the initiation of administration of commercial product of HBI-8000, whichever is earlier	Change of the study design to complete the study
64	Table 4: Schedule of Events c	Survival data will be collected every 3 months ± 2 weeks after End of Treatment until death or the end of the study, defined as 12 months after the administration of the last dose of the entire study	Survival data will be collected every 3 months ± 2 weeks after End of Treatment until death or the end of the study, defined as timing that the last Japanese subject initiates administration of the commercial product of HBI-8000.	Change of the study design to complete the study
65	Table 4: Schedule of Events m	In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn.	In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn or by completion of the whole study. If subjects cannot visit their	Change of the study design to complete the study and

Page	Change	Protocol ver. 5.0, 09 October 2019	Protocol ver. 6.0, 19 July 2021	Reason
			study site for this examination due to COVID-19 situation, investigators can skip the examination, and the assessment is to be performed approximately every 6 months ± 2 weeks. In this case, the investigator should document that fact in the medical record.	COVID-19

Protocol：HBI-8000-203 version 5.0

Protocol Table of Changes（09 October 2019）

Page	Change	Protocol ver. 4.0, 31 May 2018	Protocol ver. 5.0, 09 October 2019	Reason
1	Confidentiality Statement	Confidentiality Statement This confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.	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 HUYA Bioscience International, LLC and constitute Confidential Information under the Confidential Disclosure Agreement (CDA) between the parties. The study will be conducted according to the International Council for Harmonisation (ICH) harmonized tripartite guideline E6(R2): Good Clinical Practice, including the archiving of essential documents.	Template update
2	Signatures	[redacted]	[redacted]	Organization change and correction

Page	Change	Protocol ver. 4.0, 31 May 2018	Protocol ver. 5.0, 09 October 2019	Reason
		[redacted]	[redacted]	
3	HBI-8000-203 Protocol Synopsis	Study duration: Approximately 36 months	Study duration: Approximately 60 months	Study duration extension
3	HBI-8000-203 Protocol Synopsis	Planned study period: 4Q 2016 (first patient in) to 3Q 2018 (last patient in) 4Q 2019 study completion	Planned study period: 4Q 2016 (first patient in) to 3Q 2018 (last patient in) 4Q 2021 study completion	Study duration extension
15	1.1 Background Information	(2-Amino-4-fluorophenyl)-4-[N-[(E)-3-(3-pyridyl) acryloyl]aminomethyl] benzamide,	N-(2-Amino-4-fluorophenyl)-4-[N-[(E)-3-(3-pyridyl)acryloyl]aminomethyl]benzamide,	Correction # This correction is English Only
15	1.1 Background Information	It is now in the market under the trade name Epidaza in China. HUYA Bioscience International, LLC (HUYA) has licensed worldwide rights (excluding China) of this compound.	It is marketed under the trade name Epidaza® in China. HUYA Bioscience International, LLC (HUYABIO) has licensed worldwide rights (excluding China) of this compound.	Information update
17	1.3 Rationale for the Use of HBI-8000 for the Treatment of Cancer	Results from pre-clinical pharmacokinetics (PK) and toxicology studies in rats and dogs as well as results from a Phase 1 study conducted to date [Shenzhen Chipscreen Study Report 2008] suggest that HBI-8000 has favorable PK and safety profiles relative	Results from pre-clinical pharmacokinetics (PK) and toxicology studies in rats and dogs as well as results from a Phase 1 study conducted to date [Shenzhen Chipscreen Study Report 2008] suggest that HBI-8000 has	correction

Page	Change	Protocol ver. 4.0, 31 May 2018	Protocol ver. 5.0, 09 October 2019	Reason
		to other HDAC inhibitors.	favorable PK and safety profiles.	
20	1.5.1 Absorption	HBI-8000 is being administered two times a week continuously.	HBI-8000 was administered two times a week continuously.	correction
20	1.6 Clinical Studies	a Phase 1 study (HBI-8000-201) in patients with relapsed or refractory Non-Hodgkins Lymphoma (NHL) including PTCL and ATL was initiated in Japan in April, 2014 and has now completed. Phase 2 clinical trials are planned in patients with relapsed or refractory ATL and relapsed or refractory PTCL.	a Phase 1 study (HBI-8000-201) in patients with relapsed or refractory Non-Hodgkins Lymphoma (NHL) including PTCL and ATL was initiated in Japan in April, 2014 and has completed. Phase 2 clinical trials are on going in patients with relapsed or refractory ATL and relapsed or refractory PTCL.	Information update
22	1.8 Dose Selection and Risk Assessment	In clinical studies, treatment with HBI-8000 has been associated with myelosuppression, including thrombocytopenia, neutropenia and/or leukopenia and anemia or decreased hemoglobin. Other adverse drug reactions reported in previous clinical trials include nausea, diarrhea, fatigue/lethargy, abdominal pain, vomiting, peripheral edema, pyrexia/fever, anorexia, dizziness, and decreased appetite and transaminase increase.	In clinical studies, treatment with HBI-8000 has been associated with myelosuppression, including thrombocytopenia, neutropenia and/or leukopenia and anemia or decreased hemoglobin. Other adverse drug reactions reported in previous clinical trials include nausea, diarrhea, fatigue/lethargy, abdominal pain, vomiting, peripheral edema, pyrexia/fever, anorexia, dizziness, decreased appetite and transaminase increase.	Information updat

Page	Change	Protocol ver. 4.0, 31 May 2018	Protocol ver. 5.0, 09 October 2019	Reason
26	2.6 Study Procedures Overview	It is estimated that each patient will be on study for up to 12 months after enrollment. Assuming that 24 months are needed to meet accrual target, the study period would be of 36 months to allow efficacy and safety determination.	It is estimated that each patient will be on study for up to 36 months after enrollment. Assuming that 24 months are needed to meet accrual target, the study period would be of 60 months to allow efficacy and safety determination.	Study duration extension
47	4.2 Data Management/Coding	Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.	Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1.	Information update
59	8.0 REFERENCES	IB 2017: Investigator's Brochure for HBI-8000 (CS055, chidamide). HUYA Bioscience International, LLC, version 7, 08 July, 2017	IB 2019: Investigator's Brochure for HBI-8000 (CS055, chidamide). HUYA Bioscience International, LLC, version 9, 08 July, 2019	Information update
82	9.7 Appendix G: Signature of Investigator	This protocol is a confidential communication of HUYA Bioscience International. 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	This protocol is a confidential communication of HUYA Bioscience International, LLC. I confirm that I have read this protocol, I understand it, and I will comply with the all the terms and requirements of 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.	Correction

Page	Change	Protocol ver. 4.0, 31 May 2018	Protocol ver. 5.0, 09 October 2019	Reason
		unpublished information contained herein will be published or disclosed without prior written approval from HUYA Bioscience International.	Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from HUYA Bioscience International, LLC.	
corresponding section		HUYA	HUYABIO	Name change
corresponding section		HUYA Bioscience International	HUYA Bioscience International, LLC	Correction
corresponding section		[redacted]	[redacted]	Name change
corresponding section		IB 2017	IB 2019	Information update

Protocol：HBI-8000-203 version 4.0

Protocol Table of Changes（31 May 2018）

Page	Change	Before (Protocol ver.3.0, 27 Nov 2017)	After (Protocol ver.4.0, 31 May 2018)	Reason
2	Signatures	[redacted]	[redacted]	HUYA internal organization change
7	Synopsis Statistical procedure	Patients considered evaluable for efficacy must meet eligibility criteria and have at least one post-baseline assessment of efficacy, or who discontinue study early due to clinical PD. Efficacy should be analyzed by Full analysis set (FAS) and Per protocol set (PPS). Full analysis set is defined as patients having received at least one dose of study medication and at least one post-baseline assessment. Per protocol set is defined as patients in FAS having completed Cycle 1 treatment or discontinue study early due to clinical PD without any deviation from eligibility criteria. It should be noted that PPS includes subjects	Efficacy should be analyzed using Full analysis set (FAS) and Per protocol set (PPS). The FAS is defined as Patients meeting all eligibility criteria and having received at least one dose of study medication, and at least one efficacy assessment of disease with either imaging studies or clinical examination after receiving study medication. The PPS is defined as Patients meeting all eligibility criteria and having completed Cycle 1 treatment or discontinued study treatment during cycle 1 due to clinical PD. It should be noted that the PPS includes subjects who discontinue within Cycle 1 due to clinical PD	Clarification

		who discontinue within Cycle 1 due to clinical PD without any deviation from eligibility criteria. It is estimated that 40 evaluable patients are adequate to provide efficacy assessment. Assuming a 30% ORR in this population of 40 evaluable patients, the conclusion would be that there is a 95% chance that the ORR in this protocol population would lie between 15.8% and 44.2%.	without imaging studies to assess disease status. In addition, Patients who are assessed as Non-PTCL by the central pathology review committee should be excluded from the FAS and PPS for efficacy. The non-PTCL subjects will be included in safety analysis for the study. The primary efficacy analysis is conducted in the PPS. The Efficacy analysis using the FAS will be also reported. It is estimated that 40 evaluable patients are adequate to provide efficacy assessment. Assuming a 30% ORR in this population of 40 evaluable patients, the conclusion would be that there is a 95% chance that the ORR in this protocol population would lie between 15.8% and 44.2%. The power for showing the response rate >10% at 5% two-sided alpha in 40 patients is 89%.	
49	5.1 General Statistical Considerations	5.1 General Statistical Considerations Protocol HBI-8000-203 is an open-label, Phase 2b pivotal study evaluating HBI-8000 for regulatory approval in Japan and South	5.1 General Statistical Considerations Protocol HBI-8000-203 is an open-label, Phase 2b pivotal study evaluating HBI-8000 for regulatory approval in Japan and South	Clarification

		Korea for the indication of relapsed or refractory PTCL.	Korea for the indication of relapsed or refractory PTCL. The main analysis will be conducted for the purpose of regulatory submission of this product. The data cut-off (DCO) for the main analysis is set at the time when the last patient completes at least one post-efficacy assessment. The eCRF data by the DCO needs to be cleaned to have no unresolved queries. All independent reviews (including the Central Pathology Review, the independent radiological review, the Independent Overall Efficacy Review and review by the Data Safety Monitoring Board) by the DCO need to be completed before the main analysis. The data after the main analysis will be provided at the end of the study as a supportive material.	
49	5.2 Determination of Sample Size	The target best ORR for this study is 30%, on the basis of the ORR results that were obtained in study TG0902CDM. The 95% confidence interval (CI) for an ORR of 30% at a sample size of N=40 is expected to be between 15.8% and 44.2%.	The target best ORR for this study is 30%, on the basis of the ORR results that were obtained in study TG0902CDM. The 95% confidence interval (CI) for an ORR of 30% at a sample size of N=40 is expected to be between 15.8% and 44.2%.	Clarification

			The power for showing the response rate >10% at 5% two-sided alpha in 40 patients is 89%.	
50	5.5.2 Efficacy Population	Efficacy should be analyzed by FAS and PPS. To be evaluable for efficacy analysis, patients must meet eligibility criteria and have at least one post-baseline assessment of efficacy, or who discontinue study early due to clinical PD. FAS is defined as Patients having received at least one dose of study medication and at least one post-baseline assessment. PPS is defined as Patients in FAS having completed Cycle 1 treatment or discontinue study early due to clinical PD without any deviation from eligibility criteria. It should be noted that PPS includes subjects who discontinue within Cycle 1 due to clinical PD without any deviation from eligibility criteria.	Efficacy should be analyzed using FAS and PPS. The FAS is defined as Patients meeting all eligibility criteria and having received at least one dose of study medication, and at least one efficacy assessment of disease with either imaging studies or clinical examination after receiving study medication. The PPS is defined as Patients meeting all eligibility criteria and having completed Cycle 1 treatment or discontinued study treatment during cycle 1 due to clinical PD. It should be noted that the PPS includes subjects who discontinue within Cycle 1 due to clinical PD without imaging studies to assess disease status. In addition, Patients who are assessed as Non-PTCL by the central pathology review committee should be excluded from the FAS and PPS for efficacy. The non-PTCL subjects	Clarification

			will be included in safety analysis for the study. The primary efficacy analysis is conducted in the PPS. The Efficacy analysis using the FAS will be also reported.	
77	9.4.9.3 Evaluation of skin lesion by mSWAT	PD: Increase in mSWAT score of ≥ 25% from baseline or appearance of new lesion	PD: ≥25% increase in skin disease from baseline or New tumor mass** or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score. ** tumor mass : at least 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth	Correction of error

Protocol：HBI-8000-203 version 3.0

Protocol Table of Changes (27 Nov 2017)

Page	Change	Before (Protocol ver.2.0, 29May2017)	After (Protocol ver.3.0, 27Nov2017)	Reason
2	Signature		[redacted]	HUYA internal organization change
4	Synopsis Inclusion Criteria	2. Patients for whom at least 1 measurable lesion is confirmed by the lesion assessment at baseline; an evaluable lesion is defined as more than 1.5 cm in greatest dimension and can be followed by imaging.	2. Patients for whom at least 1 measurable lesion is confirmed by the lesion assessment at baseline; an evaluable lesion is defined <u>according to Cheson criteria 2014.</u> ~~as more than 1.5 cm in greatest dimension and can be followed by imaging.~~	Correction of error
4	Synopsis Inclusion Criteria	3.Relapsed or refractory disease after receiving ≥1 prior systemic therapy with anti-tumor agent(s) and there is no other available treatment which can be considered appropriate for patients. Systemic therapy is defined as frontline	3.Relapsed or refractory disease after receiving ≥1 prior systemic therapy with anti-tumor agent(s) and there is no other <u>standard</u> treatment which can be considered appropriate for patients. Systemic therapy is defined as frontline	Clarification

		chemotherapy or immunotherapy administered systemically.	chemotherapy or immunotherapy administered systemically.	
5	Synopsis Exclusion Criteria	4. Patients with a history of second malignancy other than disease under study. The exceptions are disease that has been treated with curative intent with no evidence of recurrence in past 2 years including÷	4. Patients with a history of second malignancy other than disease under study. The exceptions are diseases (excluding diseases listed below) that have been treated with curative intent with no evidence of recurrence in past 5 years. Furthermore, if the second malignancy is one of the following diseases that were treated with curative intent, it is only required that there is no evidence of recurrence in past 2 years:	Allow PTCL patients with second malignancy who had curative treatment with no evidence of recurrence
6	Synopsis Efficacy data	Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma [Cheson 2014]. To be included in final efficacy analyses, the histopathology diagnosis of disease will be verified by Central Pathology Review, and disease response will be confirmed by Independent Radiology Review.	Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma [Cheson 2014]. To be included in final efficacy analyses, the histopathology diagnosis of disease will be verified by Central Pathology Review, and disease response will be confirmed by Independent Radiology and Independent	Clarification of independent efficacy analysis

			Overall Efficacy Review.	
15	Introduction Background	Please refer to the Investigator's Brochure for further information on HBI-8000 [IB 2016]	Please refer to the Investigator's Brochure for further information on HBI-8000 [IB 2017]	IB was update in July 2017
19	Introduction Non-Clinical studies	Further information on non-clinical studies conducted with HBI-8000/chidamide may be found in the Investigator's Brochure [IB 2016].	Further information on non-clinical studies conducted with HBI-8000/chidamide may be found in the Investigator's Brochure [IB 2017].	IB was update in July 2017
20	Introduction Metabolism and Excretion	Further information on clinical pharmacological studies with HBI-8000/chidamide may be found in the Investigator's Brochure [IB 2016]	Further information on clinical pharmacological studies with HBI-8000/chidamide may be found in the Investigator's Brochure [IB 2017]	IB was update in July 2017
24	2.5.1 Inclusion Criteria	2. Patients for whom at least 1 measurable lesion is confirmed by the lesion assessment at baseline; an evaluable lesion is defined as more than 1.5 cm in greatest dimension and can be followed by imaging.	2. Patients for whom at least 1 measurable lesion is confirmed by the lesion assessment at baseline; an evaluable lesion is defined according to Cheson Criteria 2014. ~~as more than 1.5 cm in greatest dimension and can be followed by imaging.~~	Correction of error
24	2.5.1 Inclusion Criteria	3.Relapsed or refractory disease after receiving ≥1 prior systemic therapy with anti-tumor agent(s) and there is no other available treatment which can be	3.Relapsed or refractory disease after receiving ≥1 prior systemic therapy with anti-tumor agent(s) and there is no other standard treatment which can be	Clarification

		considered appropriate for patients. Systemic therapy is defined as frontline chemotherapy or immunotherapy administered systemically.	considered appropriate for patients. Systemic therapy is defined as frontline chemotherapy or immunotherapy administered systemically.	
25	2.5.2 Exclusion Criteria	4.Patients with a history of second malignancy other than disease under study. The exceptions are disease that has been treated with curative intent with no evidence of recurrence in past 2 years including:	4. Patients with a history of second malignancy other than disease under study. The exceptions are diseases (excluding diseases listed below) that have been treated with curative intent with no evidence of recurrence in past 5 years. Furthermore, if the second malignancy is one of the following diseases that were treated with curative intent, it is only required that there is no evidence of recurrence in past 2 years:	Allow PTCL patients with second malignancy who had curative treatment with no evidence of recurrence
26	2.6 Study Procedures Overview	Independent Radiology Review will be performed for final efficacy analyses at the completion of this study.	Independent Radiology Review and Independent Overall Efficacy Review will be performed for final efficacy analyses at the completion of this study.	Clarification of independent efficacy analysis
27	2.6 Study Procedures	At the end of the study, tumor response of each patient will be reviewed by independent radiologists in a blinded	At the end of the study, tumor response of each patient will be reviewed by independent radiologists and oncologists	Clarification of independent efficacy

	Overview	fashion to obtain best response, dates of response and progression	in a blinded fashion to obtain best response, dates of response and progression	analysis
30	2.6.8 Management and Dosage Modifications for Unacceptable Hematologic and Non-hematologic Adverse Events	If unacceptable AEs recur despite 2 dose reductions, the study treatment will be permanently discontinued and post-treatment follow up ensues.	If unacceptable AEs recur despite 2 dose reductions, the study treatment will be permanently discontinued and post-treatment follow up ensues. However, if the patients are having clinical benefit, further treatment may be considered after discussion with the sponsor.	Change to allow treatment continuation only for patients who are having clinical benefit
35	3.1.1 Primary Efficacy Endpoint	a second independent radiologist will be asked to adjudicate by way of assigning the final disease response to the determination made by either the investigators or independent radiologist for final efficacy analysis.	a second independent radiologist will be asked to adjudicate by way of assigning the final disease response to the determination made by either the investigators or independent radiologist ~~for final efficacy analysis~~. The overall efficacy review will be done by independent oncologist for final efficacy analysis.	Clarification of independent efficacy analysis

44	3.5 Independent Review		3.5.4 Independent Overall Efficacy Review To ensure consistent overall efficacy review method is applied to assess disease response across the entire study, designated independent oncologists will review sequential clinical data of individual patients including radiological assessment provided by the independent radiological review. They will assign response outcome including best response, dates of initial response and progression when applicable, based on Cheson Criteria 2014.	Clarification of independent efficacy analysis
52	5.9 Efficacy Analysis	Tumor response as assessed by imaging studies will be adjudicated by independent radiology reviewers. Tumor lesions, such as skin lesion, that cannot be monitored by imaging studies will determined by investigators only and contributed to overall disease response assessment. Both investigators	Tumor response as assessed by imaging studies will be adjudicated by independent radiology reviewers. Tumor lesions, such as skin lesion, that cannot be monitored by imaging studies will determined by independent oncology reviewers~~investigators only~~ and contributed to overall disease response	Clarification of independent efficacy analysis

		reported and independently adjudicated outcomes based on imaging studies will be reported. Primary analysis will be based on results from imaging studies confirmed by Independent Central Review. Results from investigator assessment will also be reported. In patients with skin lesion that is assessed by mSWAT, response data from imagine studies alone will be reported according to Independent Review and investigator assessment. Their overall response based on imaging studies AND mSWAT scores will be reported as investigator's assessment only.	assessment. Both investigators reported and independently adjudicated outcomes ~~based on imaging studies~~ will be reported. Primary analysis will be based on results from imaging studies and clinical data confirmed by Independent Central Review. Results from investigator assessment will also be reported. ~~In patients with skin lesion that is assessed by mSWAT, response data from imagine studies alone will be reported according to Independent Review and investigator assessment. Their overall response based on imaging studies AND mSWAT scores will be reported as investigator's assessment only.~~	
58	8.0 References	IB 2016: Investigator's Brochure for HBI-8000 (CS055, chidamide). HUYA Bioscience International, version 6, 08 July, 2016	IB 2017: Investigator's Brochure for HBI-8000 (CS055, chidamide). HUYA Bioscience International, version 7, 08 July, 2017	IB was update in July, 2017

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
All pages	Version. No, Date	（footer） Version 1.2, 30 August 2016	（footer） Version 2.0, 29 May 2017	Change of version and date
All pages	-	[redacted]	[redacted]	Information updated
p.3	Synopsis Primary objective	To determine the efficacy of HBI-8000 administered twice every week (BIW) continuously.	To determine the efficacy of HBI-8000 administered twice ~~every~~ a week (BIW) continuously	Change to the same word
p.4	Synopsis Inclusion Criteria	3. Progressive disease after receiving ≥ 1 prior systemic therapy with anti-tumor agent(s). This could include frontline chemotherapy, and mogamulizumab, or ineligible for mogamulizumab, and there is no other available treatment with proven efficacy 7. Meeting the following baseline laboratory criteria: a. Absolute Neutrophil Count >1500/μL independent of growth factor support within 7 days b. Platelets >75,000/μL independent of transfusion within 14 days c. Hemoglobin >8 g/dL independent of transfusion within 14 days d. Serum creatinine < 1.5 × ULN e. Serum aspartate aminotransferase/glutamyl oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/glutamyl pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN f. Serum Bilirubin ≤ 1.5 × ULN	3. ~~Progressive~~ Relapsed or refractory disease after receiving ≥ 1 prior systemic therapy with anti-tumor agent(s) ~~This could include frontline chemotherapy, and mogamulizumab, or ineligible for mogamulizumab~~ and there is no other available treatment ~~with proven efficacy~~ which can be considered appropriate for patients. Systemic therapy is defined as frontline chemotherapy or immunotherapy administered systemically 7. Meeting the following baseline laboratory criteria for screening: a. Absolute Neutrophil Count >1500/μL independent of growth factor support within 7 days b. Platelets >75,000/μL independent of transfusion within 14 days c. Hemoglobin >8 g/dL independent of transfusion within 14 days d. Serum creatinine < 1.5 × ULN e. Serum aspartate aminotransferase/glutamyl oxaloacetic transaminase (AST/SGOT) ~~or~~and alanine aminotransferase/glutamyl pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN f. Serum Bilirubin ≤ 1.5 × ULN	To clarify the definition Clarification of the contents Correction of the error
p.5	Synopsis Exclusion Criteria	2. Patients with known hypersensitivity to benzamide class of compounds or any of the components of HBI-8000 tablets	1. Patients in whom central nervous system lymphoma is recognized during screening (if suspected clinically, imaging study should be performed to confirm) ~~2.~~3. Patients with known hypersensitivity to benzamide class of compounds or any of the components of HBI-8000 tablets, and patients with prior exposure of HBI-8000 ~~tablets~~	Change due to reconsideration Not to investigate the activity of HBI-8000 in re-treatment setting

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		3. Patients with a second malignancy other than disease under study. The exceptions are disease that has been treated with curative intent with no evidence of recurrence in past 5 years including: a. Basal cell carcinoma of the skin b. Squamous cell carcinoma of the skin c. Cervical carcinoma in situ d. Carcinoma in situ of the breast e. An incidental histological finding of prostate carcinoma (TNM stage T1a or T1b) f. Early-stage gastric cancer treated with endoscopic mucosal resection or endoscopic submucosal dissection	~~3.~~4. Patients with a history of second malignancy other than disease under study. The exceptions are disease that has been treated with curative intent with no evidence of recurrence in past ~~5~~ 2 years including: a. Basal cell carcinoma of the skin b. Squamous cell carcinoma of the skin c. Cervical carcinoma in situ d. Carcinoma in situ of the breast e. An incidental histological finding of prostate carcinoma (TNM stage T1a or T1b) f. Early-stage gastric cancer treated with endoscopic mucosal resection or endoscopic submucosal dissection g. Thyroid cancer with differentiated histology (e.g. papillary) treated with curative intent	Indolent second malignancy with no evidence of relapse in 2 years is unlikely to interfere with the treatment of PTCL. To allow PTCL patients to enter this study from Korea where indolent thyroid cancer is common
		5. Allogeneic stem cell transplantation requiring immunosuppressant treatment within 21 days of starting the study drug or with active Graft Versus Host Disease (GVHD)	~~5.~~6. ~~Allogeneic~~ History of allogeneic stem cell transplantation ~~requiring immunosuppressant treatment within 21 days of starting the study drug or with active Graft Versus Host Disease (GVHD)~~	The effects of HBI-8000 on immune effector and regulatory cells are not yet characterized. The risks for graft rejection or exacerbated graft vs host disease cannot be estimated in patients with history of allogeneic stem cell transplantation.
		6. Organ transplantation recipients except for hematopoietic stem cell transplantation	~~6.~~7. Organ transplantation recipients except ~~for~~ autologous hematopoietic stem cell transplantation	To clarify that autologous stem cell transplantation is not considered as an organ transplantation in this protocol

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
p.6	Synopsis Excluded Prior or Concomitant Medications or Therapy: Medications And Therapy	Anti-cancer therapy other than study medication is prohibited during the study and within the following time intervals prior to the first dose of study drug: 4 weeks for anti-cancer chemotherapy and 12 weeks for anti-cancer monoclonal therapy; 6 weeks for nitrosourea or mitomycin C. Drugs known to produce significant QT prolongation or ventricular dysrhythmias are prohibited from signing informed consent through the EoT assessment. Corticosteroids prescribed for reason other than lymphoma is not considered as anti-cancer therapy in this study. Concomitant administration of HBI-8000 with drugs that significantly induce or inhibit CYP3A4, or are metabolized significantly by CYP3A4, and have a narrow therapeutic range, including St. John's wort, are prohibited.	The following drugs are prohibited. • Drugs known to produce significant QT prolongation and ventricular dysrhythmias (see Section 9.6) Prohibited from signing informed consent through the EoT assessment • Anti-cancer therapy other than study medication ~~is prohibited~~ Prohibited during the study and within the following time intervals prior to the first dose of study drug ~~and 12 weeks for anti-cancer monoclonal therapy; 6 weeks for nitrosourea or mitomycin C. Drugs known to produce significant QT prolongation or ventricular dysrhythmias are prohibited from signing informed consent through the EoT assessment. Corticosteroids prescribed for reason other than lymphoma is not considered as anti-cancer therapy in this study~~ – 4 weeks for anti-cancer chemotherapy ~~Concomitant administration of HBI-8000 with drugs that significantly induce or inhibit CYP3A4, or are metabolized significantly by CYP3A4, and have a narrow therapeutic range, including St. John's wort, are prohibited~~ – 6 weeks for nitrosourea and mitomycin C – 12 weeks for anti-cancer monoclonal antibody therapy Corticosteroid prescribed for medical conditions other than lymphoma is not considered as an anti-cancer therapy for this study, for example: chronic obstructive pulmonary disease for allergy, topical steroids for rash.	Information updated
p.6	Synopsis Treatments	Study drug is to be taken after any regular meal twice weekly, each dose separated by at least 3-4 days.	Study drug is to be taken after any regular meal twice weekly, each dose separated by ~~at least~~ 3-4 days.	Correction of the error
p.7	Synopsis Statistical Procedures	Disease diagnosis including histological subtypes will be confirmed by central pathology review conducted by independent pathologists. A patient considered evaluable for efficacy per protocol must have a baseline tumor assessment and at least 1 tumor assessment during study treatment; have received at least 1 cycle of study drug; and meet all eligibility criteria; or have discontinued study early due to clinical PD. It is estimated that 40 evaluable patients are adequate to provide efficacy assessment. Assuming a 30% ORR in this population of 40 evaluable patients, the conclusion would be that there is a 95% chance that the ORR in this protocol population would lie between 15.8% and 44.2%.	Disease diagnosis including histological subtypes will be confirmed by central pathology review conducted by independent pathologists. ~~A patient considered evaluable for efficacy per protocol must have a baseline tumor assessment and at least 1 tumor assessment during study treatment; have received at least 1 cycle of study drug; and meet all eligibility criteria; or have discontinued study early due to clinical PD.~~Patients considered evaluable for efficacy must meet eligibility criteria and have at least one post-baseline assessment of efficacy, or who discontinue study early due to clinical PD. Efficacy should be analyzed by Full analysis set (FAS) and Per protocol set (PPS). Full analysis set is defined as patients having received at least one dose of study medication and at least one post-baseline assessment. Per protocol set is defined as patients in FAS having completed Cycle 1 treatment or discontinue study early due to clinical PD without any deviation from eligibility criteria. It should be noted that PPS includes subjects who discontinue within Cycle 1 due to clinical PD without any deviation from eligibility criteria. It is estimated that 40 evaluable patients are	Clarification of the contents

<table>
<tr><th>Page</th><th>Change</th><th>Before (Protocol ver.1.2, 30Aug2016)</th><th>After (Protocol ver.2.0, 29May2017)</th><th>Reason</th></tr>
<tr><td></td><td></td><td></td><td>adequate to provide efficacy assessment. Assuming a 30% ORR in this population of 40 evaluable patients, the conclusion would be that there is a 95% chance that the ORR in this protocol population would lie between 15.8% and 44.2%.</td><td></td></tr>
<tr><td>p.13</td><td>List of abbreviations and definitions of terms</td><td>
<table>
<tr><td></td><td></td></tr>
<tr><td>AML</td><td>Acute myelogenous leukemia</td></tr>
<tr><td>ANC</td><td>Absolute neutrophil count</td></tr>
<tr><td>APL</td><td>Acute promyelocytic leukemia</td></tr>
<tr><td>ASCT</td><td>Autologous stem-cell transplant</td></tr>
<tr><td></td><td></td></tr>
<tr><td>CK</td><td>Creatine kinase</td></tr>
<tr><td>CNS</td><td>Central Nervous System</td></tr>
<tr><td>CRA</td><td>Clinical Research Associate</td></tr>
<tr><td>CRO</td><td>Contract research organization</td></tr>
<tr><td>CSR</td><td>Clinical study report</td></tr>
<tr><td>CTL</td><td>Cytotoxic T lymphocyte</td></tr>
<tr><td>DNA</td><td>Deoxyribonucleic acid</td></tr>
<tr><td>EATL</td><td>Enteropathy-associated T-cell lymphoma</td></tr>
<tr><td>EMT</td><td>Epithelial to mesenchymal transition</td></tr>
<tr><td></td><td></td></tr>
<tr><td>GVHD</td><td>Graft Versus Host Disease</td></tr>
<tr><td>HBV</td><td>Hepatitis B virus</td></tr>
<tr><td>HCV</td><td>Hepatitis C virus</td></tr>
<tr><td>HIV</td><td>Human immunodeficiency virus</td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
<tr><td>IND</td><td>Investigational new drug</td></tr>
<tr><td>K2EDTA</td><td>Dipotassium ethylene diaminetetra acetic acid</td></tr>
<tr><td>LC-MS/MS</td><td>Liquid chromatography-mass spectrometry</td></tr>
<tr><td>NKTCL</td><td>NK/T-cell lymphoma</td></tr>
<tr><td>NMR</td><td>Nuclear magnetic resonance</td></tr>
<tr><td>NOAEL</td><td>No Observed Adverse Effect Level</td></tr>
<tr><td>NSCLC</td><td>Non-small cell lung cancer</td></tr>
<tr><td>NYHA</td><td>New York Heart Association</td></tr>
<tr><td></td><td></td></tr>
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<table>
<tr><td>ADL</td><td>Activities of daily living</td></tr>
<tr><td>~~AML~~</td><td>~~Acute myelogenous leukemia~~</td></tr>
<tr><td>~~ANC~~</td><td>~~Absolute neutrophil count~~</td></tr>
<tr><td>~~APL~~</td><td>~~Acute promyelocytic leukemia~~</td></tr>
<tr><td>~~ASCT~~</td><td>~~Autologous stem-cell transplant~~</td></tr>
<tr><td>CCR4</td><td>CC chemokine receptor 4</td></tr>
<tr><td>~~CK~~</td><td>~~Creatine kinase~~</td></tr>
<tr><td>~~CNS~~</td><td>~~Central Nervous System~~</td></tr>
<tr><td>~~CRA~~</td><td>~~Clinical Research Associate~~</td></tr>
<tr><td>~~CRO~~</td><td>~~Contract research organization~~</td></tr>
<tr><td>~~CSR~~</td><td>~~Clinical study report~~</td></tr>
<tr><td>~~CTL~~</td><td>~~Cytotoxic T lymphocyte~~</td></tr>
<tr><td>~~DNA~~</td><td>~~Deoxyribonucleic acid~~</td></tr>
<tr><td>~~EATL~~</td><td>~~Enteropathy-associated T-cell lymphoma~~</td></tr>
<tr><td>~~EMT~~</td><td>~~Epithelial to mesenchymal transition~~</td></tr>
<tr><td>FAS</td><td>Full analysis set</td></tr>
<tr><td>~~GVHD~~</td><td>~~Graft Versus Host Disease~~</td></tr>
<tr><td>~~HBV~~</td><td>~~Hepatitis B virus~~</td></tr>
<tr><td>~~HCV~~</td><td>~~Hepatitis C virus~~</td></tr>
<tr><td>~~HIV~~</td><td>~~Human immunodeficiency virus~~</td></tr>
<tr><td>IB</td><td>Investigator’s Brochure</td></tr>
<tr><td>IC</td><td>Inhibitory concentration</td></tr>
<tr><td>~~IND~~</td><td>~~Investigational new drug~~</td></tr>
<tr><td>~~K2EDTA~~</td><td>~~Dipotassium ethylene diaminetetra acetic acid~~</td></tr>
<tr><td>~~LC-MS/MS~~</td><td>~~Liquid chromatography-mass spectrometry~~</td></tr>
<tr><td>~~NKTCL~~NK</td><td>~~NK/~~Natural killer~~T-cell lymphoma~~</td></tr>
<tr><td>~~NMR~~</td><td>~~Nuclear magnetic resonance~~</td></tr>
<tr><td>~~NOAEL~~</td><td>~~No Observed Adverse Effect Level~~</td></tr>
<tr><td>~~NSCLC~~</td><td>~~Non-small cell lung cancer~~</td></tr>
<tr><td>~~NYHA~~</td><td>~~New York Heart Association~~</td></tr>
<tr><td>PD</td><td>Disease progression</td></tr>
<tr><td>PMDA</td><td>Pharmaceutical and medical devices agency</td></tr>
</table>
</td><td>Modifications in abbreviation list</td></tr>
</table>

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
			PPS: Per protocol set ~~RBC: Red blood cell~~ ~~RNA: Ribonucleic acid~~ ~~R/R: Relapsed or refractory~~ ~~SUSAR: Suspected unexpected serious adverse reaction~~ TCL: T-cell lymphoma ~~T_{max}: Time to peak plasma drug concentration~~ ~~Vd/F: Apparent volume of distribution~~ ~~VEGF-R: Vascular endothelial growth factor receptor~~ ~~WBC: White blood cell~~ ~~WHO: World Health Organization~~	
p.15	1.1 Background Information	It has been approved by China FDA(CFDA) for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) in December 2014. It is now on the market under the trade name Epidaza in China.	It has been approved by China Food and Drug Administration (CFDA) for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) in December 2014. It is now ~~on~~in the market under the trade name Epidaza in China.	Correction in grammar
P16	1.3 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 HDAC (isoenzymes 6 and 10) HDACs in the nanomolar range and stimulates accumulation of acetylated histones H3 and H4 in tumor cells [Ning 2012].	HBI-8000 inhibits several cancer-associated Class I (HDAC 1, 2, 3) and one Class IIb HDAC (isoenzymes ~~6 and~~ 10) HDACs in the nanomolar range and stimulates accumulation of acetylated histones H3 and H4 in tumor cells [Ning et al 2012].	Correction of the error
p.18	1.3.1 Immunomodulatory Mechanisms Integrate with Cancer Cell Intrinsic Mechanisms of Cell Killing by HDACi	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 2013, Pan 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 causes modulation of gene regulation patterns that is consistent with that hypothesis. Genes in several functional clusters were regulated by HBI-8000 [Ning ~~2013~~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).	Correction of the error
p.20	1.5.3 Metabolism and Excretion	Nuclear magnetic resonance (19F NMR) and liquid chromatography mass spectrometry (LC-MS/MS) were used to investigate the biological conversion and material balance in 4 patients with T-cell lymphoma.	Nuclear magnetic resonance ~~(19F NMR)~~ and liquid chromatography-tandem mass spectrometry ~~(LC-MS/MS)~~ were used to investigate the biological conversion and material balance in 4 patients with TCL.	Correction of the error
p.20	1.6 Clinical Studies	For a Phase 2 dose selection, a Phase 1 study (HBI-8000-201) in patients with relapsed or refractory Non-Hodgkins Lymphoma including PTCL	For a Phase 2 dose selection, a Phase 1 study (HBI-8000-201) in patients with relapsed or refractory Non-Hodgkins Lymphoma (NHL) including PTCL and	Information updated

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		and ATL was initiated in Japan in April, 2014 and is now near completion.	ATL was initiated in Japan in April, 2014 and ~~is~~has now ~~near completion~~completed.	
p.23	2.3 Criteria for Evaluation Population Pharmacokinetic Characterization Study (applicable to participating sites and consented patients):	To obtain comparable PK data base from Japan and Korea to assess regional difference, if any, PK characterization will be required for all patients enrolled in Korea. PK sampling will be performed as detailed in Table 2 of Appendix A.	To obtain comparable PK database from Japan and Korea and to assess regional difference, if any, PK characterization will be required for all patients enrolled in Korea. PK sampling will be performed as detailed in ~~Table 2~~Table 5 of Appendix A.	Information updated
p.24	2.4 Summary of Study Design	Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma. [Cheson 2014] (see Appendix D). The rate of overall tumor response (complete response [CR], partial response [PR]), stable disease [SD], or progressive disease [PD]) will be confirmed with a second assessment repeated at least four weeks after the first response observation	Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma. [Cheson 2014] (see ~~Appendix D~~ Section 9.4). ~~The rate of overall tumor response (complete response [CR], partial response [PR]), stable disease [SD], or progressive disease [PD]) will be confirmed with a second assessment repeated at least four weeks after the first response observation.~~	Correction of the error
p.24	2.5.1 Inclusion Criteria	3. Progressive disease after receiving ≥ 1 prior systemic therapy with anti-tumor agent(s). This could include frontline chemotherapy, and mogamulizumab, or ineligible for mogamulizumab, and there is no other available treatment with proven efficacy 7. Meeting the following baseline laboratory criteria: a. Absolute Neutrophil Count >1500/μL independent of growth factor support within 7 days b. Platelets >75,000/μL independent of transfusion within 14 days c. Hemoglobin >8 g/dL independent of transfusion within 14 days d. Serum creatinine < 1.5 × ULN e. Serum aspartate aminotransferase/glutamyl oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/glutamyl pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN f. Serum Bilirubin ≤ 1.5 × ULN	3. ~~Progressive~~ Relapsed or refractory disease after receiving ≥ 1 prior systemic therapy with anti-tumor agent(s) ~~This could include frontline chemotherapy, and mogamulizumab, or ineligible for mogamulizumab~~ and there is no other available treatment ~~with proven efficacy~~ which can be considered appropriate for patients. Systemic therapy is defined as frontline chemotherapy or immunotherapy administered systemically 7. Meeting the following baseline laboratory criteria for screening: a. Absolute Neutrophil Count >1500/μL independent of growth factor support within 7 days b. Platelets >75,000/μL independent of transfusion within 14 days c. Hemoglobin >8 g/dL independent of transfusion within 14 days d. Serum creatinine < 1.5 × ULN e. Serum aspartate aminotransferase/glutamyl oxaloacetic transaminase (AST/SGOT) ~~or~~and alanine aminotransferase/glutamyl pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN f. Serum Bilirubin ≤ 1.5 × ULN	To clarify the definition Clarification of the contents Correction of the error

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
p.25	2.5.2 Exclusion Criteria		1. Patients in whom central nervous system lymphoma is recognized during screening (if suspected clinically, imaging study should be performed to confirm)	Change due to reconsideration
		2. Patients with known hypersensitivity to benzamide class of compounds or any of the components of HBI-8000 tablets	~~2.~~3. Patients with known hypersensitivity to benzamide class of compounds or any of the components of HBI-8000 tablets, and patients with prior exposure of HBI-8000 ~~tablets~~	Not to investigate the activity of HBI-8000 in re-treatment setting
		3. Patients with a second malignancy other than disease under study. The exceptions are disease that has been treated with curative intent with no evidence of recurrence in past 5 years including: a. Basal cell carcinoma of the skin b. Squamous cell carcinoma of the skin c. Cervical carcinoma in situ d. Carcinoma in situ of the breast e. An incidental histological finding of prostate carcinoma (TNM stage T1a or T1b) f. Early-stage gastric cancer treated with endoscopic mucosal resection or endoscopic submucosal dissection	~~3.~~4. Patients with a history of second malignancy other than disease under study. The exceptions are disease that has been treated with curative intent with no evidence of recurrence in past ~~5~~ 2 years including: a. Basal cell carcinoma of the skin b. Squamous cell carcinoma of the skin c. Cervical carcinoma in situ d. Carcinoma in situ of the breast e. An incidental histological finding of prostate carcinoma (TNM stage T1a or T1b) f. Early-stage gastric cancer treated with endoscopic mucosal resection or endoscopic submucosal dissection g. Thyroid cancer with differentiated histology (e.g. papillary) treated with curative intent	Indolent second malignancy with no evidence of relapse in 2 years is unlikely to interfere with the treatment of PTCL. To allow PTCL patients to enter this study from Korea where indolent thyroid cancer is common
		5. Allogeneic stem cell transplantation requiring immunosuppressant treatment within 21 days of starting the study drug or with active Graft Versus Host Disease (GVHD)	~~5.~~6. ~~Allogeneic~~ History of allogeneic stem cell transplantation ~~requiring immunosuppressant treatment within 21 days of starting the study drug or with active Graft Versus Host Disease (GVHD)~~	The effects of HBI-8000 on immune effector and regulatory cells are not yet characterized. The risks for graft rejection or exacerbated graft vs host disease cannot be estimated in patients with history of allogeneic stem cell transplantation.

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		6. Organ transplantation recipients except for hematopoietic stem cell transplantation	~~6.~~7. Organ transplantation recipients except ~~for~~ autologous hematopoietic stem cell transplantation	To clarify that autologous stem cell transplantation is not considered as an organ transplantation in this protocol
p.26	2.6 Study Procedures Overview	No central radiology review is required prior to designation of PD and treatment discontinuation. Independent Radiology Review will be performed for final efficacy analyses at the completion of this study.	No ~~central~~ independent radiology review is required prior to designation of PD and treatment discontinuation. Independent Radiology Review will be performed for final efficacy analyses at the completion of this study.	Change to the same word
p.26	2.6 Study Procedures Overview	For the first 6 patients, weekly safety laboratory tests will be obtained during the first 28 days and closely monitored for safety signals, especially for neutropenia and transaminase elevation. Central pathology review is planned at end of study before efficacy analysis. The investigator will maintain a pre-screening log to record all patients prior to screening.	For ~~the first 6~~ all patients, weekly safety laboratory tests will be obtained during the first 28 days and closely monitored for safety signals, especially for neutropenia and transaminase elevation. Central pathology review ~~is planned at end of study~~ will be completed before efficacy analysis. The investigator will maintain a pre-screening log to record all patients prior to screening.	Correction of the error
p.27	2.6.1. Screening Assessments (within 28 days prior to start of treatment)	Tumor pathology slides will be sent to central laboratory and archived for central pathology review that is planned at end of study before efficacy analysis. Screening assessments will be performed within 28 days prior to Cycle 1 Day 1 (C1D1). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to C1D1 may be used (and do not need to be repeated for screening unless they do not meet the criteria defined in the protocol).	~~Tumor~~ Unstained tumor pathology slides will be sent to pathology central laboratory and ~~archived~~ stained at the central laboratory. The images will be captured from the slides for central pathology review that is ~~planned at end of study~~ to be completed before efficacy analysis. For patients who do not have enough tumor tissue archived, a new biopsy will be requested. However, insufficient tumor tissue in archive or inability to perform new biopsy for any reason does not exclude patients from entering this study. Reasonable efforts should be made to support central pathology review. Screening assessments will be performed within 28 days prior to Cycle 1 Day 1 (C1D1). A pretreatment bone marrow test (aspiration or biopsy) would be required. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to C1D1 may be used (and do not need to be repeated for screening unless they do not meet the criteria defined in the protocol). Similarly, tumor assessment tests <2 weeks outside the 28-day window in the absence of clinical evidence of PD, the results may be accepted.	Information updated Change due to reconsideration

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		Women of childbearing potential must agree to practice effective contraceptive measures after signing informed consent. A negative serum pregnancy test will be obtained during screening. At the C1D1 visit, negative pregnancy status will be confirmed verbally before dosing and verified with blood test (see Appendix A).	Women of childbearing potential must agree to practice effective contraceptive measures after signing informed consent. A negative serum pregnancy test will be obtained during screening. ~~At the C1D1 visit, negative pregnancy status will be confirmed verbally before dosing and verified with blood test (see Appendix A).~~	Correction of the error
p.28	2.6.2. Baseline Assessments on Cycle 1 Day1 (C1D1)	Women of childbearing potential must have a negative serum pregnancy test before dosing (see Appendix A).	Women of childbearing potential must have a negative ~~serum~~ pregnancy status confirmed by serum test before dosing. If Serum pregnancy test result cannot be obtained on the same day before dosing, urine pregnancy test should be conducted additionally and the result should be confirmed before dosing (see ~~Appendix A~~ Section 9.1). Some of the pre-dose assessments except vital signs and ECG may be performed 1 day before C1D1 to accommodate scheduling requirements in the hospital.	Change due to reconsideration
p.28	2.6.3 Treatment Phase	All assessments must be performed as per the Schedule of Events (see Appendix A). Assessments scheduled on the day of study treatment should be performed prior to administration of study drug, unless otherwise noted in the schedule of assessments. Assessment of tumor response will be scheduled by end of 8 weeks, then every 8 weeks (±1 week) from C1D1. However, if a patient develops clinical signs and symptoms of disease progression, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed. If a patient discontinues study treatment before disease progression (PD) is recorded, tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn.	All assessments must be performed as per the Schedule of Events (see ~~Appendix A~~ Section 9.1). Assessments scheduled on the day of study treatment should be performed prior to ~~administration of~~ taking study drug, unless otherwise noted in the schedule of assessments. Assessment of tumor response will be scheduled by end of ~~8 weeks~~ the eighth week, then every 8 weeks (± 1 week) from C1D1. However, if a patient develops clinical signs and symptoms of PD, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed. ~~If a patient discontinues study~~ For the patients with skin lesions, decision on treatment ~~before disease progression (PD) is recorded, tumor assessments are to~~ discontinuation should be ~~performed approximately every 3 months ± 2 weeks until PD~~ based on computed tomography (CT) or ~~the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn~~ positron emission tomography (PET-CT) assessment, not Modified Severity Weighted Assessment Tool (mSWAT) scores. In other words, if imaging studies showing SD or PR while mSWAT score increases, treatment will continue.	Change due to reconsideration
p.28	2.6.4 End Of Treatment Safety Follow-Up Visit	At end of treatment safety visit, evaluations will include physical examination, vital signs, body weight, ECOG performance status, hematology, blood chemistry, urinalysis, pregnancy test (if applicable), ECG, and assessment of any ongoing adverse events.	At EoT safety visit, evaluations will include physical examination, vital signs, body weight, ECOG performance status, hematology, blood chemistry, urinalysis, pregnancy test (if applicable), ECG, and assessment of any ongoing adverse events. If a patient discontinues study treatment before PD is recorded, and if the last tumor assessment was >30 days earlier from the EoT visit, tumor assessment should be performed at EoT. In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until	Change due to reconsideration

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
			PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn.	
p.29	2.6.5. Survival Follow-up	Follow-up for survival (and tumor status in patients in whom disease progression has not yet been observed) should occur at approximately 3-month intervals after the last dose of study drug.	Follow-up for survival (and tumor status in patients in whom PD has not yet been observed) should occur at approximately 3-month intervals after the ~~last dose of study drug~~EoT visit.	Correction of the error
p.29	2.6.6. Patient Withdrawal	Study treatment may be discontinued and the patient withdrawn from the study under the following circumstances: • Unacceptable toxicity (adverse event) • Progression of the disease under study • Decision by the investigator to permanently discontinue study drug administration • Inter-current illness that would, in the judgment of the investigator, affect clinical assessments, patient safety, or follow-up significantly • Significant protocol deviations that jeopardize the usefulness of the data • Patient noncompliance	Study treatment may be discontinued and the patient withdrawn from the study under the following circumstances: • Unacceptable toxicity (AE) • Progression of the disease under study, except for isolated progression in skin lesion • Decision by the investigator to permanently discontinue study drug administration • Intercurrent illness that would, in the judgment of the investigator, affect clinical assessments, patient safety, or follow-up significantly • Significant protocol deviations that jeopardize the usefulness of the data • Repeated patient noncompliance	Clarification of the contents
p.30	2.6.8 Management and Dosage Modifications for Unacceptable Hematologic and Non-Hematologic Adverse Events	Table 1 summarizes the guidelines for dosage adjustment in the event of unacceptable Adverse Events (AEs). Two dose reductions are allowed (from 40 mg to 30mg, or from 30 mg to 20 mg). If unacceptable adverse events recur despite two dose reductions, the study treatment will be permanently discontinued and post-treatment follow-up ensues.	Table 1 summarizes the guidelines for dosage adjustment in the event of unacceptable AEs. Two dose reductions are allowed (from 40 mg to 30mg, or from 30 mg to 20 mg). If unacceptable AEs recur despite 2 dose reductions, the study treatment will be permanently discontinued and post-treatment follow-up ensues. In the event of AE, such as hematological AE-uncomplicated, necessitating two treatment interruptions, dose will be reduced when treatment resumes. However, if strongly needed for patient safety, dose can be reduced according to the investigator judgement, even if unacceptable hematological AE-uncomplicated is occurred once.	Change due to reconsideration
p.31	2.6.8 Management and Dosage Modifications for Unacceptable Hematologic and Non-Hematologic	G-CSF should be prescribed when uncomplicated grade 3 or 4 neutropenia is observed.	G-CSF ~~should~~ is recommended to be prescribed when uncomplicated grade 3 or 4 neutropenia is observed.	Clarification of the contents

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
	Adverse Events			
p.31	2.6.9 Management and Dosage Modifications for Non-Hematologic Adverse Events	In the event of Grade 3 non-hematologic adverse events (excluding isolated abnormality of laboratory values not associated with clinical significance), study medication should be held. Appropriate treatment should be initiated. Patients will be closely monitored for recovery. If the adverse events recur despite two dose reductions as applicable, study treatment should be discontinued. Study treatment should be terminated if Grade 4 non-hematologic adverse events occur.	In the event of Grade 3 non-hematologic AEs (excluding isolated abnormality of laboratory values not associated with clinical significance), study medication should be held. Appropriate treatment should be initiated. Patients will be closely monitored for recovery and managed following the Dose Adjustment Guideline. If the AEs recur despite two dose reductions as applicable, study treatment should be discontinued. Study treatment should be terminated if Grade 4 non-hematologic adverse events occur, following the Dose Adjustment Guideline	Clarification of the contents
p.32	2.7 Study Drug Administration	During this trial, patients will receive 40 mg HBI-8000 administered after any regular meal as four 10 mg tablets twice weekly (BIW) continuously.	During this trial, patients will receive 40 mg HBI-8000 administered approximately 30 minutes after any regular meal as four 10 mg tablets BIW continuously.	Clarification of the contents
p.32	2.10 Concomitant Treatments	All concomitant medications, regardless of whether they are prohibited or not, received after signing informed consent must be recorded on the eCRF.	All concomitant medications, regardless of whether they are prohibited or not, received after signing informed consent must be recorded on the eCRF. Complete information on all concurrent medications (generic name of drugs, reason for use, dosage and duration of dosing, etc.) should be documented in the original records and in the eCRF. Patients should consult their investigator prior to using medications other than the study drug, including over-the-counter medications and supplements.	To move from other section

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
p.32	2.10.1 Prohibited Medications And Therapy	Anti-cancer therapy other than study medication is prohibited during the study and within the following time intervals prior to the first dose of study drug: 4 weeks for anti-cancer chemotherapy and 12 weeks for anti-cancer monoclonal therapy; 6 weeks for nitrosourea or mitomycin C. Drugs known to produce significant QT prolongation or ventricular dysrhythmias are prohibited from signing informed consent through the EoT assessment. Corticosteroids prescribed for reason other than lymphoma is not considered as anti-cancer therapy in this study. Concomitant administration of HBI-8000 with drugs that significantly induce or inhibit CYP3A4, or are metabolized significantly by CYP3A4, and have a narrow therapeutic range, including St. John's wort, are prohibited.	The following drugs are prohibited. • Drugs known to produce significant QT prolongation and ventricular dysrhythmias (see Section 9.6) Prohibited from signing informed consent through the EoT assessment • Anti-cancer therapy other than study medication ~~is prohibited~~ Prohibited during the study and within the following time intervals prior to the first dose of study drug ~~and 12 weeks for anti-cancer monoclonal therapy; 6 weeks for nitrosourea or mitomycin C. Drugs known to produce significant QT prolongation or ventricular dysrhythmias are prohibited from signing informed consent through the EoT assessment. Corticosteroids prescribed for reason other than lymphoma is not considered as anti-cancer therapy in this study~~ – 4 weeks for anti-cancer chemotherapy ~~Concomitant administration of HBI-8000 with drugs that significantly induce or inhibit CYP3A4, or are metabolized significantly by CYP3A4, and have a narrow therapeutic range, including St. John's wort, are prohibited~~ – 6 weeks for nitrosourea and mitomycin C – 12 weeks for anti-cancer monoclonal antibody therapy Corticosteroid prescribed for medical conditions other than lymphoma is not considered as an anti-cancer therapy for this study, for example: chronic obstructive pulmonary disease for allergy, topical steroids for rash.	Information updated
p.33	2.10.2 Cautioned Medications	-	Because the anti-emetic drug Zofran (ondansetron) is well known to prolong QTc, it is prohibited on 2 occasions, Cycle 1 Day 1 and Cycle 2 Day 1 when QTc test is scheduled. Starting 24 hours before the QTc test until the QTc test is completed on the next day, patient must not take Zofran over a 2-day period. Although anti-emetics are rarely needed for HBI-8000, if anti-emetics must be used for other medical reason, alternative drug(s) should be used. If a 5-HT3 antagonist must be used to manage severe emesis refractory to other medications, dosing should be postponed until resolution of underlying medical condition. In case it is medically necessary to co-administer drugs that could interfere with CYP3A4 activity, investigators should monitor for toxicities and follow the study drug dose modifications for toxicity per study protocol. Also, St. John's wort should be used with caution.	Information updated
p.33	2.10.3 Permitted Medications	Complete information on all concurrent medications (generic name of drugs, reason for use, dosage and duration of dosing, etc.) should be documented in the original records and in the eCRF.	Sulfamethoxazole Trimethoprim use is permitted. However, when its side effects are observed, alternative antibiotics prophylaxis should be considered. ~~Complete information on all concurrent medications (generic name of drugs, reason for use, dosage and duration of dosing, etc.) should be documented in the original records and in the eCRF.~~	Information updated To move to other section

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		Patients should consult their investigator prior to using medications other than the study drug, including over-the-counter medications and supplements.	~~Patients should consult their investigator prior to using medications other than the study drug, including over-the-counter medications and supplements.~~	
p.33	2.11 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 whenever possible.	Due to potential food-drug interactions for many commonly used medications, grapefruit, grapefruit juice, Seville oranges, and any products that contain Seville oranges or grapefruit should be avoided ~~whenever~~ when possible.	Clarification of the contents
p.34	2.12 Treatment Compliance	The patient will be provided with a drug log to record date and time of administration, time of meal prior to administration, adverse events, and missed doses. The patient will be instructed to bring the drug log and study drug bottles (including any empties) to each appointment for reconciliation. At each visit, prior to dispensing study medication, previously dispensed study drug count will be confirmed by the Investigator, or authorized designee, and compliance assessed.	The patient will be provided with a drug log to record date and time of administration, time of meal prior to administration, AEs, and missed doses. ~~The~~ To verify compliance, the patient will be instructed to bring the drug log and study drug bottles (including any empties) to ~~each appointment~~ appointments scheduled for Day1 of each cycle starting with Cycle 2 for reconciliation. At each visit ~~prior to dispensing~~ when study medication is dispensed previously dispensed study drug count will be confirmed by the investigator, or authorized designee, and compliance assessed prior to dispensing new study medication.	Clarification of the contents
p.35	3.1.1. Primary Efficacy Endpoint	Tumor assessments will be performed by imaging modalities. CT, MRI, or PET scanning may be used to evaluate lesions in the neck, chest, abdomen, and pelvis; and as a baseline evaluation for patients who may have brain metastases. Evaluation of nodal lesion and extranodal lesion will be performed according to the revised criteria for response assessment in lymphoma [Cheson 2014] (see Appendix D). The definition of nodal and extranodal lesion is as following: • Nodal lesion: lymphoma that developed in lymph node and lymphoid tissue (amygdala, thymus, spleen, and Peyer's patch in small bowel) • Extranodal lesion: lymphoma that developed in non-lymphoid organ or tumor mass Tumor response will be confirmed by independent radiologists at end of study prior to final efficacy analysis. The dates of PR, CR and PD will be assessed as applicable. Initial review will be performed by one radiologist.	Tumor assessments will be performed by imaging modalities. CT, ~~MRI,~~ magnetic resonance imaging, or PET scanning may be used to evaluate lesions in the neck, chest, abdomen, and pelvis; and as a baseline evaluation for patients who may have brain metastases. The PET-CT is encouraged to be performed from baseline. However, when CT is the routine method to monitor patients according to hospital standard of care, PET-CT is not required. Evaluation of nodal lesion and extranodal lesion will be performed according to the revised criteria for response assessment in lymphoma [Cheson 2014] (see ~~Appendix D~~ Section 9.4). Skin lesions are non-target lesions. Their response will be assessed according to mSWAT, and contribute to overall response determination. ~~The definition of nodal and extranodal lesion is as following:~~ ~~• Nodal lesion: lymphoma that developed in lymph node and lymphoid tissue (amygdala, thymus, spleen, and Peyer's patch in small bowel)~~ ~~• Extranodal lesion: lymphoma that developed in non-lymphoid organ or tumor mass~~ Tumor response based on imaging studies will be confirmed with central review by independent radiologists at end of study prior to final efficacy analysis. The dates of PR, CR and PD will be assessed as applicable. Initial review will be performed by one independent radiologist.	Change due to reconsideration
p.35	3.1.2 Secondary	The secondary efficacy measures are: • ORR by disease subtype	The secondary efficacy measures are: • ORR by disease subtype	Clarification of the contents

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
	Efficacy Endpoints	• Median duration of progression-free survival (PFS) defined as the time from study enrolment to objective tumor progression or death.	• Median duration of PFS defined as the time from the first dose of study ~~enrolment~~ medication to objective tumor progression or death.	
p.36	3.2.1.2 Serious Adverse Event	Suspected transmission of an infectious agent (e.g., any organism, virus, or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE and must be reported accordingly.	~~Suspected transmission of an infectious agent (e.g., any organism, virus, or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE and must be reported accordingly~~	Correction of the error
p.39	3.2.7.1 Serious Adverse Events	All suspected unexpected serious adverse reaction (SUSAR) 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.	All suspected unexpected serious adverse reaction (SUSAR) 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~~Council for Harmonisation (ICH) E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.	Correction of the error
p.41	3.2.9 Clinical Laboratory Evaluations	Serum chemistry testing will include the following parameters: blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total bilirubin (including direct fraction if total bilirubin is abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, glucose, LDH, CKMB (creatine kinase MB fraction). Urinalysis (glucose, protein, occult blood test) will be performed by dipstick method followed by microscopic examination in the event of abnormal dipstick results.	Serum chemistry testing will include the following parameters: blood urea nitrogen, creatinine, AST, ALT, gamma-glutamyl transpeptidase, total bilirubin (including direct fraction if total bilirubin is abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, random blood glucose, LDH, creatine kinase MB fraction. Urinalysis (glucose, protein, occult blood test) will be performed by dipstick method ~~followed by microscopic examination~~, and in the event of abnormal dipstick results, additional test may be required.	Clarification of the contents Change due to reconsideration
p.42	3.2.10 Vital Signs, Physical Findings and Other Safety Assessments	The patient should be in seating position for 5 minutes before the 1st ECG is obtained, followed by 2nd and 3rd ECGs with 5 minutes between ECG measurements.	The patient should be in seating position for 5 minutes before the first ECG is obtained, followed by second and third ECGs with 5 ± 2 minutes between ECG measurements.	Change due to reconsideration
p.44	3.5.1. Data Safety Monitoring Board	A DSMB has been established to monitor the safety observed during the conduct of this study. For the first 6 patients, weekly safety laboratory tests should be obtained during the first 28 days and closely monitored for safety signals, especially the neutropenia and transaminase elevation	A DSMB has been established to monitor the safety observed during the conduct of this study. For ~~the first 6~~ all patients, weekly safety laboratory tests should be obtained during the first 28 days and closely monitored for safety signals, especially the neutropenia and transaminase elevation	Correction of the error
p.44	3.5.2 Independent Radiology Review	To ensure consistent methodology is applied to assess disease response across the entire study, designated radiologists will review sequential imaging studies of individual patients.	To ensure consistent ~~methodology~~ radiology method is applied to assess disease response across the entire study, designated radiologists will review sequential imaging studies of individual patients.	Clarification of the contents

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
p.44	3.5.3 Central Pathology Review	3.5.3 Independent Pathology Review To ensure consistent diagnosis of PTCL subtypes, a panel of pathologists with appropriate expertise will review pathology slides from archival tumor specimens or biopsy as applicable. The techniques, such as immunohistochemistry staining, will be according to standard of practice at the end of study.	3.5.3 ~~Independent~~ Central Pathology Review To ensure consistent diagnosis of PTCL subtypes, a panel of pathologists with appropriate expertise will review pathology slides from archival tumor specimens or biopsy as applicable. The techniques, such as immunohistochemistry staining, will be according to standard of practice ~~at~~ using agreed methodology, no later than the end of study.	Change to the same word Clarification of the contents
p.50	5.5.2 Efficacy Population	All patients meeting eligibility criteria who receive at least one cycle of HBI-8000, have at least one post-baseline assessment of efficacy, or who discontinue study early due to clinical PD.	~~All~~ Efficacy should be analyzed by FAS and PPS. To be evaluable for efficacy analysis, patients ~~meeting~~ must meet eligibility criteria ~~who receive at least one cycle of HBI-8000,~~ and have at least one post-baseline assessment of efficacy, or who discontinue study early due to clinical PD. ~~PK~~ FAS is defined as Patients having received at least one dose of study medication and at least one post-baseline assessment. PPS is defined as Patients in FAS having completed Cycle 1 treatment or discontinue study early due to clinical PD without any deviation from eligibility criteria. It should be noted that PPS includes subjects who discontinue within Cycle 1 due to clinical PD without any deviation from eligibility criteria.	Clarification of the contents
p.51	5.6 Patient Characteristics	Demographic and baseline characteristics of patients will be summarized using descriptive statistics: • Age • Gender • Race • Ethnicity • ECOG Performance Status • Prior therapies • Stage of Disease • Other baseline characteristics as collected on the eCRF	Demographic and baseline characteristics of patients will be summarized using descriptive statistics: • Age • Gender • Race • Ethnicity • ECOG Performance Status • Prior therapies ~~• Stage of Disease~~ • Other baseline characteristics as collected on the eCRF	Correction of the error
p.52	5.9 Efficacy Analysis	Response rate endpoints (ORR and ORR by disease subtype) will be summarized by number and percentage of patients meeting the definition of ORR along with the corresponding exact 95% confidence intervals. Tumor response will be adjudicated by independent reviewers. Both investigators reported and independently adjudicated outcomes will be reported.	Response rate endpoints (ORR and ORR by disease subtype) will be summarized by number and percentage of patients meeting the definition of ORR along with the corresponding exact 95% CI. Tumor response as assessed by imaging studies will be adjudicated by independent radiology reviewers. Tumor lesions, such as skin lesion, that cannot be monitored by imaging studies will determined by investigators only and contributed to overall disease response assessment. Both investigators reported and independently adjudicated outcomes based on imaging studies will be reported. Primary analysis will be based on results from imaging studies confirmed by Independent Central Review. Results from	Change due to reconsideration

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		Time-to event endpoints (PFS, DOR, and OS) will be summarized by Kaplan-Meier methods (median, 95% CI, number of events, number censored and Kaplan-Meier figures).	investigator assessment will also be reported. In patients with skin lesion that is assessed by mSWAT, response data from imagine studies alone will be reported according to Independent Review and investigator assessment. Their overall response based on imaging studies AND mSWAT scores will be reported as investigator's assessment only. In addition, the ORR will be analyzed according to histology subtypes of PTCL. The subtypes reported by Central pathology review for each patient will be used for such analysis. Time-to event endpoints (PFS, DOR, and OS) for entire study population will be summarized by Kaplan-Meier methods (median, 95% CI, number of events, number censored and Kaplan-Meier figures).	
p.54	6.3 Patient information and informed consent	Written consent must be given by the patient and/or guardian, after the receipt of detailed information on the study. The investigator is responsible for ensuring that informed consent is obtained from each patient or guardian 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.	Written consent must be given by the patient and/or the legal guardian, after the receipt of detailed information on the study. The investigator is responsible for ensuring that informed consent is obtained from each patient or the legal guardian 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.	Clarification of the contents
p.55	6.4 Patient 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. Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a Sponsor or representative physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files.	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. Information about study subjects will be kept confidential and managed according to the regulatory requirements. ~~Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a Sponsor or representative physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files.~~	Clarification of the contents
p.56	7.1 Administrative structure	The administrative structure and study organization is presented in Appendix F.	The administrative structure and study organization is presented in ~~Appendix F~~ Protocol addendum.	Information updated
p.58	8.0 References	Cheson BD, Fisher RI, Barrington SF, et al. (2014) Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 32(27):3059–3067.	Cheson BD, Fisher RI, Barrington SF, et al. ~~(2014)~~ Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol~~-~~. 2014;32(27):3059–3067.	Modifications in the references

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		Oken, M.M., Creech, R.H., Tormey, D.C., et. al. Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.	Oken, ~~M.M.,~~MM, Creech, R.H., Tormey, D.C., et. al. Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol-. 1982;5:649-655~~, 1982~~.	
			Olsen, EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneious Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment Center. J Clin Oncol. 2011;29:2598-2607.	
		Piekarz RL, Frye R, Prince HM, et al: Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 117:5827-5834, 2011.	~~Piekarz RL, Frye R, Prince HM, et al: Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 117:5827-5834, 2011.~~	
		Piekarz RL, Frye R, Turner M, et al: Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 27: 5410-5417, 2009.	~~Piekarz RL, Frye R, Turner M, et al: Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 27: 5410-5417, 2009.~~	
		Schemies J, Sippl W, and Jung M. Histone deacetylase inhibitors that target tubulin. Cancer Lett. 2009 Mar 4. [Epub ahead of print] PubMed PMID: 19268440.	Schemies J, Sippl W, and Jung M. Histone deacetylase inhibitors that target tubulin. Cancer Lett. ~~2009 Mar 4. [Epub ahead of print] PubMed PMID: 19268440~~2009 Aug 8;280(2):222-32	
		Shen L and R Pili, Class I histone deacetylase inhibition is a novel mechanism to target regulatory T cells in immunotherapy, OncoImmunology, 2012, 1(6), 948–950.	~~Shen L and R Pili, Class I histone deacetylase inhibition is a novel mechanism to target regulatory T cells in immunotherapy, OncoImmunology, 2012, 1(6), 948–950.~~	
			Shi P, Yin T, Zhou F, et al. Valproic acid sensitizes pancreatic cancer cells to natural killer cell-mediated lysis by upregulating MICA and MICB via the PI3K/Akt signaling pathway. BMC Cancer. 2014; 14:370.	
		Shi Y, Dong M, Hong X, Zhang W, et al. Results from a multicentre, openlabel, pivotal Phase II study of chidamide in relapsed or refractory peripheral T-Cell lymphoma. Annals of Oncology 26, 1766-1771.	Shi Y, Dong M, Hong X, ~~Zhang W,~~ et al. Results from a multicentre, openlabel, pivotal Phase II study of chidamide in relapsed or refractory peripheral T-Cell lymphoma. Annals of Oncology 2015;26~~,~~:1766-1771~~, 2015~~.	

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<tr><th>Page</th><th>Change</th><th>Before (Protocol ver.1.2, 30Aug2016)</th><th>After (Protocol ver.2.0, 29May2017)</th><th>Reason</th></tr>
<tr><td></td><td></td><td>Yamaguchi K. Survey and comprehensive measures of HTLV-1 infection and related diseases in Japan (Summary research report 2009).</td><td>~~Yamaguchi K. Survey and comprehensive measures of HTLV-1 infection and related diseases in Japan (Summary research report 2009).~~</td><td></td></tr>
<tr><td>p.61</td><td>9.1 Appendix A: HBI-8000-203 Schedule of Events

Table 4 Schedule of Events</td><td>
<table>
<tr><td colspan="2">Cycle 1</td><td></td><td></td><td></td><td colspan="2">Cycle 2[a]</td><td></td><td>Cycle ≥ 3[a]</td></tr>
<tr><td colspan="2">1</td><td>8±2</td><td>15±2</td><td>22±2</td><td colspan="2">1</td><td>15</td><td>1</td></tr>
<tr><td>Pre-dose</td><td>3.5 hrs</td><td></td><td></td><td></td><td>Pre-dose</td><td>3.5 hrs</td><td></td><td>Pre-dose</td></tr>
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<tr><td colspan="2">1</td><td>8±2</td><td>15±2</td><td>22±2</td><td colspan="2">1±4</td><td>15±4</td><td>1±7</td></tr>
<tr><td>Pre-dose[p]</td><td>3.5 hrs</td><td></td><td></td><td></td><td>Pre-dose</td><td>3.5 hrs</td><td></td><td>Pre-dose</td></tr>
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Table 4 Schedule of Events</td><td>
<table>
<tr><td></td><td>Cycle ≥ 3[a]</td><td>EoT[b]</td><td>Survival F/U[c]</td></tr>
<tr><td>Tumor assessment [m]</td><td>X[m]</td><td></td><td></td></tr>
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<table>
<tr><td></td><td>Cycle ≥ 3[a]</td><td>EoT[b]</td><td>Survival F/U[c]</td></tr>
<tr><td>Tumor assessment [m]</td><td>X[m]</td><td>X[m]</td><td>X[m]</td></tr>
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<tr><td>p.62</td><td>9.1

Table 4 Schedule of Events Footnote</td><td>Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BIW, twice weekly; BUN, blood urea nitrogen; CNS, central nervous system; CT, computed tomography; Disc, discontinuation; ECG, electrocardiogram; ECOG- PS, ECOG Performance Status, EoT, end of treatment; F/U, follow-up; GGT, gamma-glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus;INR, international normalized ratio; MRI, magnetic resonance imaging; PK, pharmacokinetic; PT, prothrombin time;</td><td>Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BIW, twice weekly; BUN, blood urea nitrogen; ~~CNS, central nervous system; CT, computed tomography; Disc, discontinuation;~~ ECG, electrocardiogram; ECOG~~- PS, ECOG Performance Status;~~ Eastern Cooperative Oncology Group; EoT, end of treatment; F/U, follow-up; GGT, gamma-glutamyl transpeptidase; ~~HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus;~~INR, international normalized ratio; ~~MRI, magnetic resonance imaging~~LDH, lactate dehydrogenase; mSWAT, Modified Severity-Weighted Assessment Tool; PET-CT, positron emission tomography-computer tomography; PCR, polymerase chain reaction; PK, pharmacokinetic; PT, prothrombin time;</td><td>Correction of the error</td></tr>
<tr><td>p.62</td><td>9.1

Table 4 Schedule of Events Footnote</td><td>a. All visits and assessments may be performed ± 5 days to accommodate unforeseen delays, holidays, or vacations.

d. Drug administration BIW for 4 weeks; On the days of scheduled visits, patient should take study drug after receiving confirmation from Investigator to continue study treatment.</td><td>a. Cycle/Day designation is based on actual calendar days after the first dose. All visits and assessments may be performed ± ~~5~~7 days to accommodate unforeseen delays, holidays, or vacations.

d. Drug administration BIW for 4 weeks ; On the days of scheduled visits that is the same as the dosing scheduled day, patient ~~–~~should take study drug after receiving confirmation from investigator to continue study treatment.</td><td>Change due to reconsideration
Clarification of the contents</td></tr>
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Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		g. Pre-dose and post dose at 3.5 ± 0.5 hours in triplicates, 5 minutes between 1st and 2nd, 2nd and 3rd ECGs, on Day 1 of Cycles 1 and 2.	g. Pre-dose and post dose at 3.5 ± 0.5 hours in triplicates, 5 ± 2 minutes between 1st and 2nd, 2nd and 3rd ECGs, on Day 1 of Cycles 1 and 2.	
		i. BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium and glucose, LDH, CKMB (creatine kinase MB fraction).	i. BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium and random blood glucose, LDH, CKMB (creatine kinase MB fraction).	
		j. Urinalysis: dipstick (glucose, protein, occult blood test) followed by microscopic examination if abnormal results.	j. Urinalysis~~: dipstick~~ (glucose, protein, occult blood test) ~~followed~~will be performed by ~~microscopic examination if~~dipstick method, and in the event of abnormal dipstick results, additional test may be required.	
		l. Confirmatory test at the Cycle 1 Day 1 (C1D1) visit should be done before dosing at the local laboratory. Only for women of childbearing potential, including those who have had a tubal ligation. Only at EoT visit, Serum and Urine are both acceptable.	l. Only for women of childbearing potential, including those who have had a tubal ligation. Confirmatory test at the Cycle 1 Day 1 (C1D1) visit should be done before dosing at the local laboratory. ~~Only for women of childbearing potential, including those who have had a tubal ligation.~~ If Serum pregnancy test result cannot be obtained on the same day before dosing, urine pregnancy test should be conducted additionally and the result should be confirmed before dosing. Only at EoT visit, Serum and Urine are both acceptable.	
		m. Complete tumor assessment of all lesions by radiographic or other modality. Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma [Cheson 2014]. Assessment of tumor response will be scheduled by end of 8 weeks, then every 8 weeks (±1 week) from C1D1, However, if a patient develops clinical signs and symptoms of disease progression, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed. If a patient discontinues study treatment before disease progression (PD) is recorded, tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn.	m. Complete tumor assessment of all lesions by radiographic or other modality. Baseline bone marrow test (aspiration or biopsy) is required. Response and progression for PTCL will be evaluated according to the revised criteria for response assessment in lymphoma [Cheson 2014~~].~~], however, PET-CT is not required but encouraged. Skin lesions, if present, will be assessed by mSWAT and contribute to overall tumor response determination by investigators. Assessment of tumor response will be scheduled by end of ~~8 weeks~~the 8th week, then every 8 weeks (± 1 week) from C1D1, However, if a patient develops clinical signs and symptoms of disease progression, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed. If a patient discontinues study treatment before disease progression (PD) is recorded, and if their last tumor assessment was >30 days earlier from EoT visit, tumor assessment should be performed at EoT. In these patients, further tumor assessments are to be performed approximately every 3 months ± 2 weeks until PD or the start of new cancer therapy whichever occurs first, unless consent to study participation is withdrawn.	

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
		o. Day 1 of cycles 3- 6 pre-dose PK sample only.	o. Day 1 of cycles 3 to 6 pre-dose PK sample only. p. Some of the pre-dose assessments except vital signs and ECG may be performed one day before C1D1 to accommodate scheduling requirements in the hospital.	
p.67	9.4 Appendix D	Appendix D: Revised Criteria for Response Assessment in Lymphoma	Appendix D: ~~Revised Criteria for Response~~Method of Efficacy Assessment in Lymphoma	Title updated
p. 67	Section 9.4 Appendix D	Appendix D: Revised Criteria for Response Assessment in Lymphoma	The following sections are added in Appendix D Preamble 9.4.1 Evaluation at Screening Figure 1: Selection of Lesions 9.4.2 Imaging 9.4.2.1 *Definition of lesion which can be used for efficacy assessment (evaluable lesion)* 9.4.2.2 *Definition of lesion which cannot be used for efficacy assessment (non-evaluable lesion)* 9.4.2.3 *Definition of Measurable Lesion (common with nodal and extranodal lesion)* 9.4.2.4 *Definition of Non-measurable lesion* 9.4.2.5 *Nodes or Extranodal Lesions That Split When Disease Is Responding* 9.4.2.6 *Nodes or Extranodal Lesions That Become Confluent When Disease Is Progressing* 9.4.3 Selection of Target Lesions	Information updated Change due to reconsideration

Page	Change	Before (Protocol ver.1.2, 30Aug2016)	After (Protocol ver.2.0, 29May2017)	Reason
			9.4.4 Definition and Selection of Non-target Lesion 9.4.5 Evaluation of Skin Lesion 9.4.6 Evaluation by Modified Severity-Weighted Assessment Tool (mSWAT) (Olsen et al. 2011) Table 1: Modified Severity Weighted Assessment Tool (mSWAT) Figure 2: Percentage BSA of each Part of Human Body 9.4.7 Presence or absence of splenomegaly 9.4.8 Evaluation of infiltration to bone marrow 9.4.9 Postdose Evaluation 9.4.9.1 *Evaluation of target lesion* 9.4.9.3 *Evaluation of skin lesion by mSWAT*	
p. 79	Section 9.6 Appendix F	Appendix F: Study Organization	~~Appendix F: Study Organization~~	New protocol addendum is created and all the information is described in.
p. 79	Section 9.6 Appendix F	-	Appendix F: Drugs known to produce significant QT prolongation and ventricular dysrhythmias	Information updated