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 Adult T Cell Lymphoma (ATL)**
Protocol Number:	**HBI-8000-210**
Version:	**5.0**
Date of Protocol:	**21 September 2018**
Replaced Protocol:	**17 July 2018 / Version 4.0**
Product:	**HBI-8000**
Study Phase:	**2b**
Sponsor:	**HUYA Bioscience International, LLC** **12531 High Bluff Drive, Suite 138** **San Diego, CA 92130** **United States of America**

HBI-8000-210 Protocol Synopsis

Name of Sponsor/Company:	HUYA Bioscience 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 Adult T-Cell Lymphoma (ATL)	
Protocol No:	HBI-8000-210	
Study site(s):	25 to 35 sites in Japan	
Study duration: Approximately 36 months		**Phase:** 2b
Planned study period: 4Q 2016 (first patient in) to 4Q 2018 (last patient in) 4Q 2019 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 twice a week (BIW) continuously

Endpoints:

Primary:

- Objective response rate (ORR; Complete Response [CR] + Unconfirmed CR [CRu) + 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)

Study Design:

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

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 or unacceptable toxicities are observed despite appropriate dose reduction or treatment interruption.	
Number of patients:	Eighteen Japanese patients with relapsed or refractory ATL evaluable for efficacy. To ensure meeting this target, an estimated 22 patients would be enrolled in anticipation that some patients may not complete study treatment.
Entry Criteria:	**Inclusion** 1. Histopathological or cytological diagnosis of ATL confirmed as seropositive for anti-Human T-lymphotrophic Virus type-I (HTLV-1) antibody 2. Acute, lymphoma or unfavorable chronic types. The unfavorable chronic type is defined by the presence of at least 1 of the following: serum albumin <3.5 g/dL, lactic dehydrogenase (LDH) >300 U/L, or blood urea nitrogen (BUN) >25 mg/dL. The patient must have at least 1 of measurable lesion, or evaluable lesion in either of peripheral blood or skin 3. Relapsed or refractory disease after receiving prior systemic therapy with mogamulizumab, or ≥1 prior systemic therapy with cytotoxic chemotherapy in case of intolerance/contraindication for mogamulizumab. And there is no other standard treatment which can be considered appropriate for patients 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-cancer 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 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 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 intercurrent 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 deoxyribonucleic acid (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 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 ATL within 4 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 Appendix E) Prohibited from signing informed consent through the end of treatment (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 or mitomycin C - 4 weeks for anti-cancer monoclonal antibody therapy Corticosteroids prescribed for medical conditions other than lymphoma is not considered as 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 to 4 days. Treatment will continue until PD in the absence of unacceptable toxicity.
Efficacy Data:	Response and progression for ATL will be evaluated according to the criteria of the International Consensus Meeting [Tsukasaki 2009] (modified).
Safety Data:	All patients who receive at least 1 dose of HBI-8000 will be evaluable for safety. AE severity (Grade) will be defined according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Serial electrocardiograms (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 schedule of events. All reported AEs will be collected, evaluated, and coded using Medical Dictionary for Regulatory Activities (MedDRA).

Statistical Procedures:

Statistical analysis for all safety and efficacy 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, and 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.

Efficacy should be analyzed by 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. For efficacy determination, 18 patients evaluable for efficacy per protocol criteria are required. To ensure meeting this target, 22 patients would be enrolled if 20% of patients are assumed not to complete required study treatment or evaluations for efficacy determination. 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.

The target best ORR for this study is 30%, on the basis of the ORR results that were obtained in study TG0902CDM. The power for showing the response rate >5% at 5% two-sided alpha in 18 patients is 80%.

Any patient that has 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
AE	Adverse event
ALT	Alanine aminotransferase
ALT/SGPT	Alanine aminotransferase/glutamyl pyruvic transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCT	Autologous stem cell transplant
AST	Aminotransferase/glutamyl oxaloacetic transaminase
AST/SGOT	Aminotransferase/glutamyl oxaloacetic transaminase
ATL	Adult T-cell leukemia/lymphoma
AUC	Area under the curve
BIW	Twice a week
BUN	Blood urea nitrogen
CFDA	China FDA
CI	Confidence interval
CKMB	Creatine kinase MB fraction
C_{max}	Peak plasma drug concentration
CNS	Central Nervous System
CR	Complete response
CRA	Clinical Research Associate
CRO	Contract research organization
CRu	Unconfirmed complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CTL	Cytotoxic T-lymphocyte
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
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
HDAC	Histone deacetylase

HDACi	Histone deacetylase inhibitor
HSP	Heat shock protein
IC_{50s}	inhibitory concentrations
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mSWAT	Modified Severity-Weighted Assessment Tool
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural killer cell
NKG2D	Natural killer group 2D
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PPS	Per protocol set
PT	Prothrombin time
PTCL	Peripheral T-cell lymphoma
QTcF	QT interval corrected by heart rate, using Fridericia's Correction Formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SiRNA	Small interfering RNA
SOP	Standard operating procedures
TEAE	Treatment-emergent adverse event
TIW	Three times a week
T_{max}	Time to peak plasma drug concentration
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

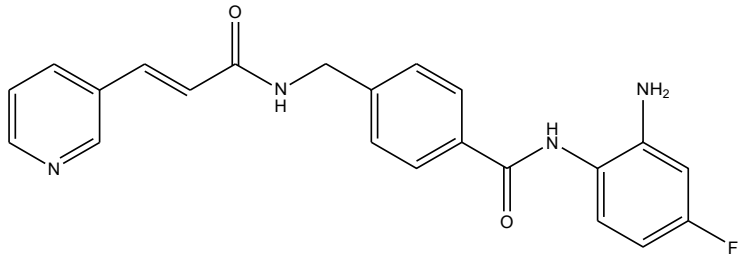
1.0 INTRODUCTION

1.1 Background Information

HBI-8000 (CS055, chidamide), N-(2-Amino-4-fluorophenyl)-4-[N-[(E)-3-(3-pyridyl) acryloyl]aminomethyl] benzamide, is a member of the benzamide class of histone deacetylase inhibitors (HDACi) designed to block primarily the catalytic pocket of Class I HDACs. It was discovered by Shenzhen Chipscreen Biosciences Co., Ltd. (Chipscreen) in Shenzhen, China, using a computer-aided rational drug design [Yin 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 now on the market under the trade name Epidaza in China. HUYA Bioscience International, LLC (HUYA) has licensed worldwide rights (excluding China) of this compound. The development programs in solid tumors and hematologic malignancies are underway. The terms HBI-8000 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, 390.41)

HBI-8000 is an orally bioavailable, low-nanomolar inhibitor of cancer-associated histone deacetylase (HDAC) enzymes with favorable pharmacology and safety profiles relative to existing benzamide and non-benzamide HDACi. Please refer to the Investigator's Brochure for further information on HBI-8000 [IB 2017].

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 2006; Minucci 2006; Glaser 2007; Rasheed 2007; Rasheed 2008; Haberland 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 2006; Nakagawa

2007; Fritzsche 2008; Weichert 2008a; Weichert 2008b]. Small interfering RNA (siRNA)-mediated inhibition of HDAC isoenzyme 1 or 3 resulted in anti-proliferative effects, and HDAC2 inhibition using siRNA sensitized tumor cells to apoptosis [Haberland 2009].

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

Several HDAC inhibitors have been approved by the FDA for the treatment of T-cell lymphoma, 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 2 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).

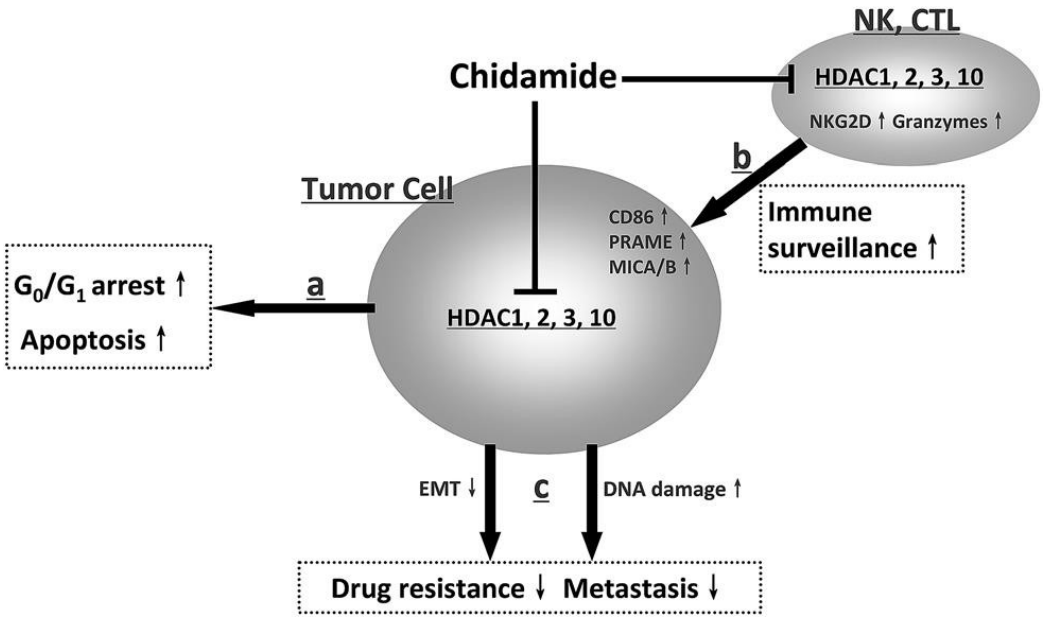
Preliminary results have suggested that HDACi are active in non-small cell lung cancer and breast carcinoma when combined with other anti-tumor agents, however, their activity as single agent in solid tumors has not been demonstrated in clinical trials [Blumenschein 2008, Crump 2008, Modesitt 2008, Vansteenkiste 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 1 Class IIb HDAC (isoenzyme 10) HDACs in the nanomolar range and stimulates accumulation of acetylated histones H3 and H4 in tumor cells [Ning 2012]. In vitro, HBI-8000 inhibits the growth of a wide variety of tumor cell lines, with 50% inhibitory concentrations (IC_{50}s) in the single-digit micromolar range. HBI-8000 is non-toxic to non-transformed cells (IC_{50}s $\geq$ 100 micromolar) [Ning 2012]. In vivo HBI-8000 has demonstrated dose-dependent anti-tumor activity against human xenograft models [Ning 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 2008] suggest that HBI-8000 has favorable PK and safety profiles relative to other HDAC inhibitors.

Emerging data suggest that there are 3 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 natural killer cell (NK)-mediated and CD8+ Cytotoxic T-lymphocyte (CTL) -mediated antigen-specific anti-tumor immunity, and partial reversal of epithelial mesenchymal transition and drug resistance of tumor cells as described in Figure 2. However, the activation of NK- and antigen-specific CTL-mediated cellular anti-tumor immunity appears only to be associated with the benzamide type of selective HDACi such as HBI-8000 (Figure 2).

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



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

It has been theorized that cancer 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 immunocyte function as well. Some of these cancer cell intrinsic defects are reversible and the promise of epigenetic regulators like HDACi is that they can concurrently target multiple aberrant or compensatory signaling pathways found in cancer cells by restoring the genome, and by extension the transcriptome, to 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 2012, 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 anti-tumor 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 NK group 2D (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 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 2015].

1.4 Non-clinical 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 1 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 2017]. 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 pharmacokinetics of chidamide was evaluated in 33 patients with T-cell lymphoma. After a single oral administration of 30 mg of chidamide after any regular meal, the average time to peak plasma drug concentration (T_{max}) 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 pharmacokinetic parameters of chidamide were evaluated in 19 T-cell lymphoma patients administered with multiple doses of chidamide. Compared to that of single dose patients, the AUC_{0-t} value increased 1.8-fold after the eighth 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 pharmacokinetics 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 pharmacokinetics was studied in seven patients with T-cell lymphoma. 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 potential 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 to 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 is being administered 2 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 (LC-MS/MS) were used to investigate the biological conversion and material balance in 4 patients with T-cell lymphoma. Seven days after a single dose of 30 mg, 80.2 ± 9.5% of chidamide was excreted in urine and feces, the majority of which occurred within the first 72 hours. Chidamide was eliminated predominantly (67.6 ± 12.7%) through urine, and the remaining 12.6 ± 7.7% through feces. In the excreted chidamide, the parent drug form was 37.6 ± 9.2% of total dosage, of which 39.4% was through urine and 86.9% was through feces. There were also 5 main metabolites, products of mono-oxidation at different positions and hydrolysis of benzamide bond through 2 major metabolic pathways.

Further information on clinical pharmacological studies with HBI-8000/chidamide may be found in the Investigator's Brochure [IB 2017].

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.

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 23 December 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 ATL in Japan. For a Phase 2 dose selection, a Phase 1 study (HBI-8000-201) in patients with relapsed or refractory 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.

1.7 Rationale for Use in Disease under Study – Adult T-Cell Lymphoma (ATL)

Adult T-cell leukemia/lymphoma (ATL) is a PTCL caused by latent infection of human T-cell lymphotropic virus type 1 (HTLV-1). There is a long latency period, up to 4 decades, between infection and the onset of ATL, and only 5% of HTLV-1 infected individuals develop ATL [Tobinai 2009]. There are an estimated 1.2 million HTLV-1 carriers in Japan. The annual incidence of ATL among HTLV-1 carriers ranges from 0.05% to 0.1%. According to a 2009 survey, there were approximately 1100 new ATL cases diagnosed annually in Japan. Approximately 700 to 1,000 patients die yearly in Japan from ATL [Yamaguchi 2002, Yamaguchi 2009].

The outcome for ATL patients in general is poor. The 3-year overall survival has been approximately 24% with conventional chemotherapy. There is an unmet need for efficacious treatment [Yoshimitsu 2015]. Over the last decade, the outcome of autologous hematopoietic stem cell transplantation has been disappointing. Allogeneic stem cell transplantation has been considered as potential approach to achieve long term disease remission. However, it is only applicable to a small fraction of patients who are younger, having achieved sufficient disease control, and with an appropriate stem cell donor [Utsunomyia 2001, Hishizawa 2010].

In Japan, Mogamulizumab (an anti-CCR4 monoclonal antibody) was approved in 2012 based on a multicenter Phase II study in 28 patients with relapsed, aggressive CCR4+ATL. However, despite initial response, albeit in a fraction of patients, the disease invariably relapsed or became refractory [Ishida 2003, Ishida 2012]. Therefore, it is of critical importance to develop additional new therapies for ATL, especially for relapsed or refractory ATL (R/R ATL).

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, 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 (G-CSF). The Grade 3 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 and 5 achieving partial response (PR). Furthermore, 4 of the 5 patients with R/R ATL enrolled in this Phase 1 study achieved PR, 1 had stable disease (SD). Although the sample size is small and firm conclusion must not be made, it is worth pointing out that the 4 PRs were observed in ATL patients initially treated at 40 mg while the SD patient were treated at 30 mg. Thus, it was felt that such an efficacy signal in patients with strong unmet medical needs warrants further investigation. Upon review of risk and benefit in totality, the 40 mg BIW schedule was selected as the starting dose for the Phase 2. The current study is designed to further evaluate the efficacy of HBI-8000 in R/R ATL.

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 post-dose evaluations of peripheral blood, skin lesions, nodal and extranodal lesions by imaging studies every 8 weeks. Evaluation of nodal lesions and extranodal lesions will be performed according to the criteria of the International Consensus Meeting [Tsukasaki 2009] (modified) (See Appendix D).

Primary:

- Objective response rate (ORR; Complete Response [CR] + Unconfirmed CR [CRu] + PR

Secondary:

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

Exploratory:

- Median duration of overall survival (OS)

Safety Endpoints:

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

2.4 Summary of Study Design

This is a Phase 2b, open-label, non-randomized, single-arm study to evaluate the safety, and efficacy of HBI-8000 40 mg BIW in patients with relapsed or refractory ATL (R/R ATL). 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.

Response and progression for ATL will be evaluated according to the criteria of the International Consensus Meeting [Tsukasaki 2009] (see Appendix D).

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. Histopathological, or cytological diagnosis of ATL confirmed as seropositive for anti-Human T-lymphotrophic Virus type-I (HTLV-I) antibody
2. Acute, lymphoma or unfavorable chronic types. The unfavorable chronic type is defined by the presence of at least 1 of the following: serum albumin <3.5 g/dL, lactic dehydrogenase (LDH) >300 U/L or blood urea nitrogen (BUN) >25 mg/dL. The patient must have at least 1 of measurable lesion, or evaluable lesion in either of peripheral blood or skin.
3. Relapsed or refractory disease after receiving prior systemic therapy with mogamulizumab, or ≥1 prior systemic therapy with cytotoxic chemotherapy in case of intolerance/contraindication for mogamulizumab. And there is no other standard treatment which can be considered appropriate for patients.
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 at screening.
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
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 intercurrent 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 ATL within 4 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 (SD or a response) in the absence of unacceptable toxicity. Progressive disease 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 (EoT) 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 the neutropenia and transaminase elevation.

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. 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 in the study. The investigator will maintain a screening log to record all patients screened.

Local radiology reports on disease status will guide investigator's decision on-study treatment, including discontinuation. At the 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).

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 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 ATL diagnosis in accordance with the WHO revised classification [WHO 2008] and treatment history. 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 contraceptive measures after signing informed consent. A negative serum pregnancy test will be obtained during screening.

2.6.2 Baseline Assessments on Cycle 1 Day 1 (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 Appendix A). 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 Appendix A). 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 fourth week, eighth week, then every 8 weeks (± 1 week) from C3D1. However, if a patient develops clinical signs and symptoms of PD, or unacceptable toxicity occurs, tumor assessment may be performed sooner as needed.

2.6.4 End of Treatment Safety Follow-up Visit

All patients receiving at least 1 dose of HBI-8000 and discontinuing treatment for any reason except death will be evaluated approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, 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 AEs. 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.

Patients with HBI-8000-related AEs of Grade ≥ 2 observed at the EoT visit should be followed-up and monitored 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 12 months after the administration of the last dose of the entire study. The first subsequent anti-cancer 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 decide 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
- 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 non-compliance
- 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 Appendix A) or before the initiation of

new cancer treatment, 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 2 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 • Thrombocytopenia Grade 3 or 4 upon observation	Hold dose, initiate G-CSF, once resolved to ≤1 within 2 weeks, resume at same dose. 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

The 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 2 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 (Table 1).

2.7 Study Drug Administration

During this the trial, patients will receive 40 mg of 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, Labeling, 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 containing a desiccant pack, and a cotton coil. Each bottle contains 26 tablets. 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.

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 Appendix E)
  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
- 4 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, anti-diarrheal, anti-allergy agents, rash reliever, anti-hypertensive 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.

2.10.4 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.

2.11 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 dates and times 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 Day 1 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. Non-compliance to drug amount is defined as taking <75% or >125% of study medication during a cycle. Non-compliance 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 the investigator, a patient is unable to follow instruction, study treatment should be discontinued.

2.12 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 the ORR, evaluated using the criteria of the International Consensus Meeting [Tsukasaki 2009] (modified) (see Appendix D).

Tumor response will be confirmed with central review by independent radiologist at end of study based on imaging studies prior to final efficacy analysis. The dates of PR, CR and PD will be assessed as applicable. Initial review will be performed by 1 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 (acute, lymphoma, and unfavorable chronic type)
- 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 OS

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 1 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 dyscrasia 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 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, Grade ≥2 AEs 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 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 resolve by that time will be recorded as "ongoing" on the eCRF.

3.2.3 Pre-existing Conditions

A pre-existing condition will not be reported as an AE unless the condition worsens by at least 1 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.

Progressive disease 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 selfcare ADL. Selfcare 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 reaction 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, 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, LDH, creatine kinase MB fraction.

Urinalysis (glucose, protein, occult blood) 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 for safety 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 pre-dose and 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 first ECG is obtained, followed by second and third ECGs with 5 ± 2 minutes between ECG measurements.

3.3 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. The sum of Screening and Cycle 1 is shown in Table 2. Assuming each patient would receive up to 6 Cycles of treatment, subsequent cycles will have blood collections for safety tests on Day 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 60 mL (Table 3). For patients receiving treatment Cycle 7 and beyond, 10.5 mL blood will be drawn for safety tests. The total blood collection volume for EoT will be approximately 6 mL for safety tests.

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
HTLV-1 antibodies	1	1	1
Hepatitis B virus tests	1	2	2
Hepatitis C virus tests	1	4	4
Total			50.5

Table 3: Cycle 2-Cycle 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			58.5

3.4 Independent Review

3.4.1 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 ATL and are not associated with this study. They are assisted by 1 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.

3.4.2 Independent Radiology Review

To ensure consistent radiology method is applied to assess disease response cross 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 Tsukasaki Criteria. They will be blinded to the local radiology findings. Should discrepancy between assessments by independent radiologist (s) and site occur, a second independent radiologist will adjudicate by selecting assessment from either site or first independent radiologist for final analysis.

3.4.3 Independent Overall Efficacy Review

To ensure consistent overall efficacy determination, 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 Tsukasaki Criteria.

4.0 QALITY 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 (CRO), [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 site 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, 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.

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

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. 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-8000-210 is a Phase 2b Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Oral HBI-8000 in Patients with Relapsed or Refractory Adult T-Cell Lymphoma (ATL). 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 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, and efficacy 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 Statistical Analysis System 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 HUYA Biosciences. 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, 18 patients evaluable for efficacy per protocol criteria are required. To ensure meeting this target, 22 patients would be enrolled if 20% of patients are assumed not to complete required study treatment or evaluations for efficacy determination. 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.

The target best ORR for this study is 30%, on the basis of the ORR results that were obtained in study TG0902CDM. The power for showing the response rate >5% at 5% two-sided alpha in 18 patients is 80%.

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 1 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.

5.5.3 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:
    - AE
    - 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 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 + CRu + PR

Secondary Endpoints:

- ORR by disease subtype (acute, lymphoma, and unfavorable chronic type)
- 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.

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).

5.10 Safety Analysis

All patients who receive 1 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

AEs 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.

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.

GCP 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.

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. investigational new drug (IND), the principal investigator must comply with U.S. FDA IND 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.

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 F). By signing the protocol, the investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any 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-8000-210 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,e]		BIW[f]					BIW[f]			BIW[f]		
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[g]	X	X			X		X		X	X	X	
12 Lead ECG (Safety)	X									X	X	
12 Lead ECG (QTc)[h]		X	X				X	X				
Hematology [i]	X	X		X	X	X	X		X	X	X	
Coagulation [j]	X	X			X		X			X		
Chemistry [k]	X	X		X	X	X	X		X	X	X	
Urinalysis [l]	X	X									X	
Hepatitis B/C virus, and HTLV-I Antibody tests [m]	X											
Serum pregnancy test (if applicable)[n]	X	X									X	
Tumor assessment [o]	X						X			X[o]	X[o]	X[o]
Patient survival; new cancer therapies												X
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/Uh, follow-up; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; LDH, lactate dehydrogenase; mSWAT, Modified Severity-Weighted Assessment Tool; PCR, polymerase chain reaction; 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, or before the initiation of new cancer treatment, whichever is earlier.

c Survival data will be collected every 3 months ± 2 weeks after EoT until death or the end of the study, defined as 12 months after the administration of the last dose of the entire study.

d 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 Drug administration BIW for 4 weeks

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

g 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.

h 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 C1D1 and C2D1

i Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count.

j Coagulation tests (PT, aPTT, and INR).

k 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

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

m Hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody and hepatitis C virus antibody will be analyzed at screening. Hepatitis B surface antigen-positive or hepatitis C virus antibody positive patients are excluded from the study. 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 the study.

n Only for women of childbearing potential, including those who have had a tubal ligation. Confirmatory test at the 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.

o Complete tumor assessment of all lesions by radiographic or other modality. Response and progression for ATL will be evaluated according to the International Consensus Meeting [Tsukasaki 2009]. CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations. CT/MRI of the head at screening for patients who are suspected to have CNS metastases. Assessment of tumor response will be scheduled by end of the 4th week, the 8th week, then every 8 weeks (± 1 week) from C3D1. 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 treatment before 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.

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.

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

Table 5: 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

Table 6: 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: Tumor Response Criteria

9.4.1 Method of Efficacy Assessment

Overall response will be assessed based on evaluation at screening and post-dose evaluation including complete tumor response assessments (peripheral blood, skin lesions, nodal and extranodal lesions) and on Day 1 of subsequent cycles for peripheral blood and skin lesions. Imaging studies such as CT to evaluate nodal and extranodal lesions will performed by end of the 4th week, the eighth week, then every 8 weeks (± 1 week) from C3D1 . 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 treatment before 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.

9.4.2 Evaluation at Screening

At screening, lesion will be evaluated by imaging (CT), hematology test (white blood cell [WBC] count, absolute lymphocyte count, and abnormal lymphocyte count (% and absolute count) and bone-marrow test (bone-marrow aspiration or biopsy). 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)

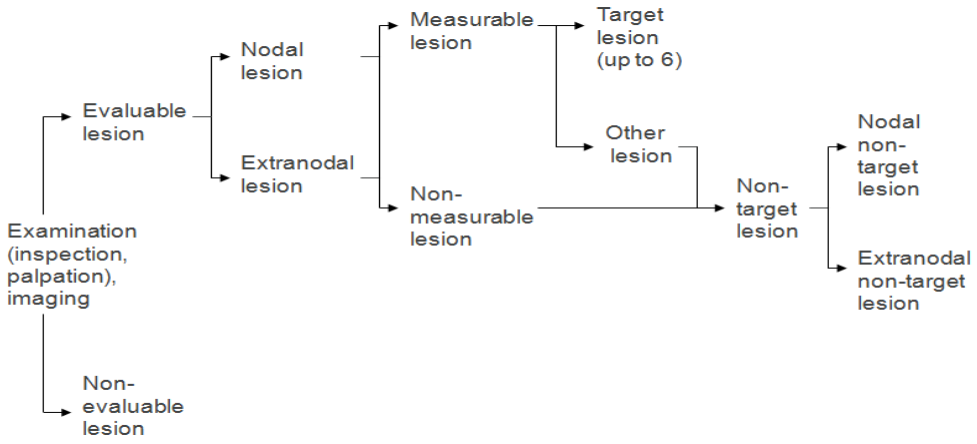
In addition, evaluable lesions are categorized into the following:

- measurable lesion
- non-measurable lesion

Next, target lesions (up to 6 lesions) are selected from measurable lesions.

Non-measurable lesions and other measurable lesions are deemed as non-target lesions.

Figure 3: Selection of Lesions



9.4.2.1 Evaluation of Nodal Lesion and Extranodal Lesion

Evaluation of nodal lesion and extranodal lesion will be performed according to the Criteria for Adult T-Cell Leukemia-Lymphoma (Tsukasaki 2009).

The definition of nodal and extranodal lesion is as following:

- Nodal lesion: lymphoma that developed in lymph node and lymph tissue (amygdala, thymus, spleen, and Peyer's patch in small bowel)
- Extranodal lesion: lymphoma that developed in non-lymphoid organ or tumor mass.

9.4.2.1.1 Imaging

Before the start of study drug administration, evaluation by CT images of neck, chest, abdomen, and groin that are taken by a pitch of 1 cm or less (as for neck image, a pitch of 5 mm or less will be preferred) will be performed. As a general rule, contrast enhanced CT should be used. However, in case contrast enhanced CT cannot be performed because the subject has a history of adverse drug reaction caused by contrast agent or a current history of renal dysfunction, and in case the lesions of the subject are evaluable by non-contrast enhanced CT, plain CT is permitted.

If evaluation by other imaging is needed according to the type of lesion, additional imaging will be permitted (e.g., MRI).

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

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

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

Non-evaluable lesion is defined as nodal lesion with the size equal to or less than 1.5 cm by long dimension on sectional image of CT at screening and extranodal lesion that cannot be followed by imaging.

9.4.2.1.4 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 size by Long dimension over 1.5 cm on sectional image of CT
- Definitely measurable by 2 orthogonal dimensions (long dimension and its orthogonal dimension) on sectional image of CT

9.4.2.1.5 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 size over 1.5 cm by long dimension on sectional image of CT, but not definitely measurable by 2 dimensions (long dimension and its orthogonal dimension)
- Extranodal lesion: All lesions that can be followed by imaging, but do not meet the definition of measurable lesion

9.4.2.1.6 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 should be selected
- Lesions are selected up to 6 in descending order by long dimension size on sectional image of CT. If measurable lesions are less than 6, all measurable lesions are selected

The lengths of long dimension (cm) and short dimension (cm) which is orthogonal to long dimension are measured, and their product (2-dimension product: cm^2) will be calculated.

The sum of all 2-dimension products (cm^2) will be calculated and defined as the sum of 2-dimension products at screening.

2-dimension product of each target lesion (cm^2) = long dimension (cm) × short dimension (cm) which is orthogonal to long dimension

The sum of 2-dimension products at screening = 2-dimension product (target lesion 1) + 2-dimension product (target lesion 6)

9.4.2.1.7 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 non-target lesions. If any tumor lesions are found through gastrointestinal endoscopy, the lesion is to be evaluated as extranodal non-target lesion.

9.4.2.2 Evaluation of Skin lesion

In case tumor lesion on skin exists, the lesion is considered as a skin lesion which can be used for efficacy evaluation be evaluated. 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 evaluated according to Severity-Weighted Assessment Tool (Stevens et al 2002): Revised Edition (mSWAT).

9.4.2.2.1 Evaluation by Modified Severity-Weighted Assessment Tool (mSWAT)

A total of body surface area (%BSA) of each part is defined in Table 7 and Figure 4 (e.g., head 7, neck 2, 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).

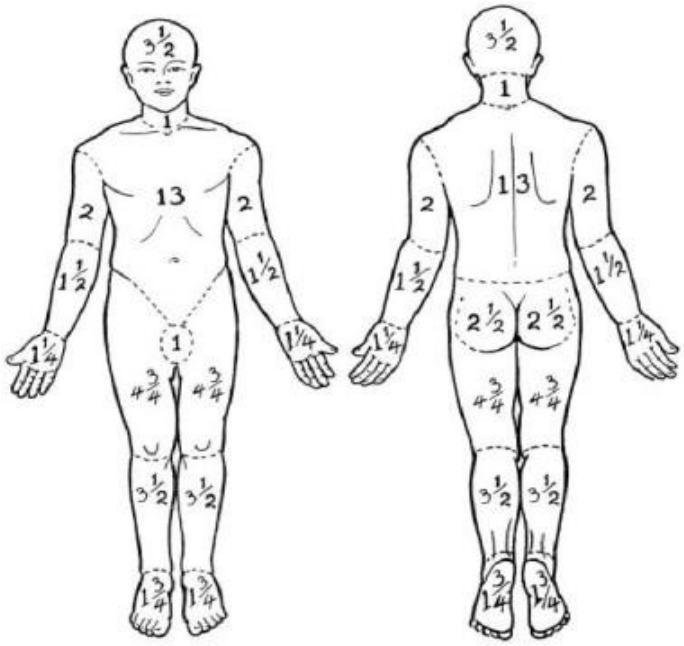
mSWAT score = (%TBSA of patch × 1) + (%TBSA of plaque × 2) + (%TBSA of tumor mass and ulcer × 4)

Table 7: BSA in Body Region

Part	%BSA Patch	%BSA Plaque	%BSA Tumor mass or ulcer	%BSA Normal	Total %BSA of each part
Head					7
Neck					2
Anterior truck					13
Posterior truck					13
Breech					5
Genital area					1
Brachial region					8
Antebrachial region					6
Both hand region					5
Femoral region					19
Reg region					14
Both foot region					7
%TBSA of each lesion					100

Patch: plain erythema
Plaque: raised lesion
Tumor mass: nodosity lesion with swell over 1 cm
Ulcer: lesion with a deficit of skin surface, such as deficit of total epidermis or a part of upper area of hypodermis

Figure 4: %BSA of each part of human body



9.4.2.3 Evaluation of peripheral blood lesion

Peripheral blood lesion which can be used for efficacy assessment is defined as the findings of abnormal lymphocyte which meet following criteria, by hematological test:

- The rate of abnormal lymphocyte to WBC is equal to or more than 5% and the absolute count of abnormal lymphocyte is equal to or more than $1000/mm^3$.

9.4.2.4 Presence or absence of hepatic enlargement and splenomegaly

Presence or absence of hepatic enlargement and splenomegaly which are considered to be caused by infiltration of lymphocyte is assessed by CT.

9.4.2.5 Evaluation of infiltration to bone-marrow

Infiltration to bone-marrow will be evaluated by bone-marrow aspiration or biopsy and 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.

9.4.3 Post-dose Evaluation

9.4.3.1 Evaluation of nodal and extranodal lesion

Computed tomographgy imaging will be performed by the same method as screening.

9.4.3.1.1 Evaluation of target lesion

Efficacy for target lesion will be assessed by calculating reduction rate (A) and growth rate (B) of the sum of 2-dimension products according to the following formula:

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

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

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

(C) = sum of 2-dimension products

Criteria for assessment of anti-tumor effect on target lesion are as follows:

CR: Absence of enlarged lymph node, AND disappearance of all extranodal lesions.

CRu: Reduction rate of the sum of 2-dimension products of ≥75%, but presence of residual lesion

PR: Reduction rate of the sum of 2-dimension products of ≥50% and <75%

SD: Effect not reached PR, but not PD

PD: Growth rate of the sum of 2-dimension products of ≥50%

9.4.3.1.2 Evaluation of nodal non-target lesion

Criteria for assessment of tumor shrinkage effect on nodal non-target lesion are as follows:

Normal: Absence of enlarged lymph node (long dimension over 1.5 cm) in any lymph node area.

Non-growth: Presence of enlarged lymph node, but absence of enlarged lymph node which showed apparent growth*2 in comparison with minimum value on and after screening

Growth: Presence of enlarged lymph node which showed apparent growth[*2] in comparison with minimum value on and after screening

Non-evaluable: Presence of lymph node area which cannot be evaluated

[*2] Apparent growth is, only as a guide, the growth of long dimension ≥50%, but measurement on image is not necessary.

9.4.3.1.3 Evaluation of extranodal non-target lesion

Criteria for assessment of tumor shrinkage effect on extranodal target lesion are as follows. If gastrointestinal lesion is found at screening, endoscopy will be performed. Confirming by biopsy is recommended when a subject is assessed as "disappearance".

Disappearance: All extranodal non-target lesion disappear on image. OR, extranodal non-target lesion has been absent since the start of study drug administration.

Non-growth: Presence of at least 1 extranodal non-target lesion, but absence of extranodal non-target lesion which showed apparent growth[*3] in comparison with minimum value after screening

Growth: Presence of extranodal non-target lesion which showed apparent growth[*3] in comparison with minimum value after screening

Non-evaluable: Presence of non-evaluable extranodal non-target lesion

[*3] Apparent growth is, only as a guide, the growth of long dimension ≥50%, but measurement on image is not necessary.

9.4.3.2 Evaluation of skin lesion by mSWAT

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

CR: Absence of skin lesion[*4]

PR: Reduction in mSWAT score of ≥50% from screening, but presence of residual skin lesion

SD: Effect not reached PR, but not PD

PD: ≥25% increase in skin disease from baseline or New tumor mass*[5] 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.

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

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

9.4.3.3 Evaluation of peripheral blood lesion (Abnormal lymphocyte)

Evaluation of peripheral blood lesion will be performed by using the values obtained at the screening and Day 1 of subsequent cycles. Criteria for assessment of hematological efficacy by evaluation of peripheral abnormal lymphocyte are as following:

CR: The rate of abnormal lymphocyte versus WBC <5%, AND absolute count of lymphocyte[*6] <4000 /mm^3.

PR: Reduction in absolute count of peripheral abnormal lymphocyte ≥50% in comparison with the count at screening

SD: Effect not reached PR, but not PD

PD: Absolute count of abnormal lymphocyte* ≥4000 /mm^3, AND increase in absolute count of abnormal lymphocyte ≥50% in comparison with the minimum value after screening.

[*6] Total count of normal lymphocyte and abnormal lymphocyte

9.4.3.4 Evaluation of hepatic enlargement and splenomegaly

Criteria for efficacy on tumor shrinkage of hepatic enlargement and splenomegaly which are considered to be caused by lymphocyte infiltration are as follows:

Disappearance: Both of hepatic enlargement and splenomegaly are disappeared (shrank on image and impalpable), OR absence of enlargement since screening

Non-exacerbation: Residual hepatic enlargement or splenomegaly, but no apparent exacerbation

Exacerbation: Apparent exacerbation of any of hepatic enlargement or splenomegaly in comparison with the minimum status after screening

Non-evaluable: Any of hepatic enlargement or splenomegaly is not evaluable

9.4.3.5 Evaluation of bone-marrow infiltration

Evaluation of bone-marrow infiltration by bone-marrow aspiration or biopsy after the start of study drug administration will be performed only in case the possibility of CR in overall response based on other endpoints occurred in subjects who were evaluated as “positive” when undetermined” at screening. The same category used for evaluation at screening will be used for assessment (see Section 9.4.2.5).

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.

9.4.3.6 Presence or absence of new lesion

Presence or absence of new lesion which do not exist at screening will be assessed.

Table 8: Response Criteria for Adult T-Cell Leukemia-Lymphoma (Tsukasaki 2009)

Response	Definition	Lymph Nodes	Extranodal Masses	Spleen, Liver	Skin	Peripheral Blood	Bone Marrow
Complete remission*	Disappearance of all disease	Normal	Normal	Normal	Normal	Normal†	Normal
Uncertified complete remission*	Stable residual mass in bulky lesion	≥75% decrease‡	≥75% decrease‡	Normal	Normal	Normal†	Normal
Partial remission*	Regression of disease	≥50% decrease‡	≥50% decrease‡	No increase	≥50% decrease	≥50% decrease	Irrelevant
Stable disease*	Failure to attain complete/partial remission and no progressive disease	No change in size	No change in size	No change in size	No change in size	No change	No change
Relapsed disease or progressive disease	New or increased lesions	New or ≥50% increase§	New or ≥50% increase§	New or ≥50% increase	≥50% increase	New or ≥50% increase‖	Reappearance
Not assessable							

- † Provided that <5% of flower cells remained, complete remission was judged to have been attained if the absolute lymphocyte count, including flower cells, was $<4 \times 10^9$/L.
- ‡ Calculated by the sum of the products of the greatest diameters of measurable disease.
- § Defined by ≥50% increase from nadir in the sum of the products of measurable disease.
- ‖ Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of $>4 \times 10^9$/L.

9.5 Appendix E: 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.

Table 9: Drugs Known To Produce Significant QT Prolongation

List of Drugs Produce 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

List of Drugs Produce QT Prolongation		
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

Table 10: 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

9.6 Appendix F: 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 Adult T-Cell Lymphoma (ATL)

PROTOCOL NO: HBI-8000-210

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 unpublished information contained herein will be published or disclosed without prior written approval from HUYA Bioscience International.

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: _____

_____

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