1827. Oral HDAC Inhibitor HBI-8000 in Japanese Patients with Non–Hodgkin Lymphoma (NHL): Phase I Safety and Efficacy Results

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INTRODUCTION

HBI-8000 (chidamide) is a novel, oral Class I (HDAC 1,2,3) and Class II (HDAC 10) selective HDAC inhibitor (HDACi) with anti-tumor activity through various mechanisms of action, including epigenetic reprogramming, leading to the direct inhibition of cell cycle and induction of apoptosis.

Preclinically, HBI-8000 induced cell cycle arrest and apoptosis in both primary ATL cells and ATL cell lines. Indirectly, HBI-8000 has demonstrated immunomodulatory activities that include the epigenetic activation of natural killer (NK) cell, cytotoxic T cell (CTL) and tumor target cell genes that enhance the activities of these immune effector cells.

Clinical development was initiated in China, and subsequently in the U.S. and Japan. In Dec 2014 it was approved in China for the treatment of relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL) under the trade name Epidaza. In the registration trial, 79 patients with R/R PTCL were evaluable for response assessment. Epidaza was administered at 30 mg twice a week (BIW) orally. Objective responses were confirmed by scans repeated 4 weeks after initial observation of response and by an independent radiology review committee. The overall response rate (ORR) was 28% including 14% of CR/CRu (Shi et al., 2014) with favorable safety profile. Clinical development is ongoing in Japan, Korea, and the U.S. We present the preliminary results from a recently completed phase I trial in Japan with advanced NHL (NCT02697552). The drug for this study is manufactured in the U.S.

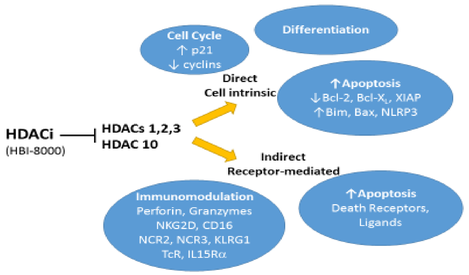


Figure 1. Mechanism of action of HBI-8000

METHODS AND STUDY DESIGN

Table 1. Demographics and Clinical Characteristics

Characteristic	30 mg BIW (N=7*)		40 mg BIW (N=7)	
	N	%	N	%
Gender				
Female	3	50%	4	57%
Male	4	67%	3	43%
Diagnosis				
Peripheral T-Cell Lymphoma (PTCL)	2	33%	-	-
Adult T-Cell Lymphoma (ATL)	1	17%	4	57%
Diffuse Large B-Cell Lymphoma (DLBCL)	2	33%	1	14%
Follicular Lymphoma (FL)	-	-	2	29%
Cutaneous T-Cell Lymphoma (CTCL)	1	17%	-	-
Mucosa-associated lymphoid tissue (MALT) B-cell lymphoma	1	17%	-	-
Age (year)				
Median	72.1		63.0	
Range	(65-81)		(57-76)	
Ann Arbor Stage				
I	1 (17%)		-	
II	2 (33%)		3 (43%)	
III	-		1 (14%)	
IV	4 (67%)		1 (14%)	
ECOG Performance Status				
0	4 (67%)		4 (57%)	
1	3 (50%)		3 (43%)	

*7 enrolled and 6 evaluable for DLT

This phase I trial enrolled patients at 7 centers in Japan from June 2014 to October 2016. Inclusion criteria: histologically or cytologically proven NHL and no other standard therapy was available. The primary endpoint was the MTD based on the frequency of dose-limiting toxicities (DLTs) observed within 28 days of the first dose. Secondary endpoints included pharmacokinetic (PK) and anti-tumor activity. Three dose levels: 30 mg, 40 mg and 50 mg were planned. Conventional 3+3 design was used for dose escalation. HBI-8000 was administered approximately 30 minutes after a meal (e.g., breakfast). DLT was defined according to CTC AE version 4.03: Grade 4 hematologic toxicity including investigation (lab values) only; Grade 3 febrile neutropenia; Grade 3 thrombocytopenia with hemorrhage or requiring platelet transfusion; any other Grade ≥ 3 non-hematologic toxicity, except for the diarrhea, nausea or vomiting before optimal supportive care was administered; hypertension that could be controlled by up to 2 additional medications; Grade 1 cardiac troponin I increased on each of 3 consecutive days. A data safety monitoring board was established to monitor study safety.

Table 2. Summary of Adverse Events in at least 1 Patient

Adverse Events	All Grade				Grade 3, 4			
	30 mg BIW N=6		40 mg BIW N= 7		30 mg BIW N=6		40 mg BIW N= 7	
	N	%	N	%	N	%	N	%
All	6	100%	7	100%	4	67%	5	71%
Investigations								
Anemia	5	83%	0	0%	1	17%	0	0%
Neutrophil decrease	3	50%	2	29%	2	33%	2	29%
White blood cells decrease	4	67%	1	14%	1	17%	1	14%
Platelet decrease	5	83%	7	100%	0	0%	2	29%
Lymphocyte Count decrease	1	17%	0	0%	1	17%	0	0%
Triglyceride increase	0	0%	1	14%	0	0%	1	14%
Hyperuricemia	2	33%	0	0%	0	0%	0	0%
Weight Loss	1	17%	2	29%	0	0%	0	0%
Creatine Phosphokinase (CPK) increased	1	17%	0	0%	1	17%	0	0%
Gastrointestinal disorders total								
Nausea	1	17%	2	29%	0	0%	0	0%
Diarrhea	2	33%	1	14%	0	0%	0	0%
Abdominal pain	1	17%	1	14%	0	0%	0	0%
General disorders total								
Pyrexia/Fever	0	0%	2	29%	0	0%	1	14%
Fatigue/Malaise	2	33%	1	14%	0	0%	0	0%
Metabolism and nutrition disorders total								
Anorexia	1	17%	1	14%	0	0%	0	0%
Hypokalemia	2	33%	0	0%	0	0%	0	0%
Hypocalcemia	0	0%	2	29%	0	0%	0	0%
Nervous system disorders total								
Dysgeusia	2	33%	1	14%	0	0%	0	0%

Safety. Thirteen out of 14 pts were evaluable for the 1st cycle DLT assessment (6 pts in the 30 mg, 7 pts in the 40 mg cohort). As shown in Table 2, the treatment was well tolerated, and adverse event (AE)s were predominantly hematological.

The 30 mg dose cohort completed with no DLT in 6 pts. The hematologic grade 3/4 toxicities observed in 7 patients in 40 mg dose cohort were leukopenia (2 pts, 29%), neutropenia (3 pts, 43%), and thrombocytopenia (3 pts, 43%). Non-hematologic AEs included fatigue, nausea, diarrhea, decreased appetite, erythema and pyrexia. Cardiovascular assessments including serial ECGs and troponin assessments did not reveal clinically significant findings. In the 40 mg cohort, 1 pt had asymptomatic and transient grade 4 neutropenia; the other developed grade 3 alanine transaminase (ALT) increase noted in routine laboratory tests. According to protocol defined DLT, dose escalation ceased at 40 mg and 3 more patients were added to the 30 mg cohort. The grade 4 neutropenia promptly resolved with the administration of G-CSF and the grade 3 ALT elevation resolved with dose interruption.

RESULTS

Best Response

By Dose

- 40 mg cohort (N=7)
  1 CR (1/7: 14%), 5 PR (5/7: 71%), 1 SD (1/7: 14%). No PD.
  Overall response rate (ORR) (CR+PR): 6/7 (86%).
- 30 mg BIW dose cohort (N=6): ORR: 1 PR (1/6: 17%).
  4 SD (4/6: 67%)

By Disease Types

- ATL (N=5) 4 PR, 1 SD
- DLBCL (N=3) 1 PR, 1 SD, 1PD
- FL (N=2) 1 CR, 1 PR

Fig 2. Disease Response Summary

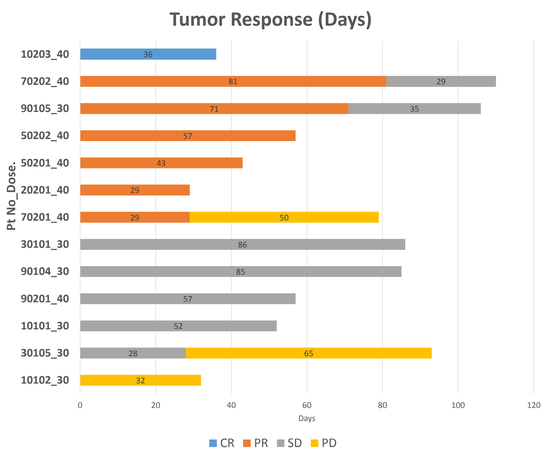


Table 3. Response Based on Investigator Assessment

Pt ID	Dose mg	Lympho-ma	Best Response	# of Doses Received	Reason for Discontinuation	# of Prior Treatment Regimen(cycle)
010101	**30**	**PTCL**	**SD**	**8**	AE G2	CHOP or A+CHP(6)
010102	**30**	**DLBCL**	**PD**	**8**	PD	R-CHO(5), RB(6), radiotherapy
030101	**30**	**ATL**	**SD**	**34**	PD	Mogamulizumab+CHOP (5)
010203	40	FL	CR	47	Complete 6 cycles CR + 2 cycles	CHOP (6)
020201	**40**	**FL**	**PR**	**52**	AE G1	R-Benda(6), Zevalin(1)
050201	**40**	**ATL**	**PR**	**21**	AE G3	CHOP (2), ImmunoTherapy
050202	**40**	**ATL**	**PR**	**6**	AE G4	CHOP-14(3), mLSG15(1), Radiotherapy
702010	**40**	**ATL**	**PR**	**16**	PD	mLSG15 (1), UV Light therapy, Mogamulizumab (8), hydrocortisone
070202	**40**	**ATL**	**PR**	**13**	AE	mLSG15 (6), lenalidomide, Mogamulizumab (8)
090201	**40**	**DLBCL**	**SD**	**8**	consent withdrawal	R-CHOP(14), CPA(1), CHASER(2), MPEC(6), ICE(2), GCD(4)
030105	**30**	**CTCL**	**SD**	**9**	PD	CHOP(6), Mogamulizumab(1), radiotherapy
090104	**30**	**MALT**	**SD**	**14**	AE G3	CHOP(6)
090105	**30**	**DLBCL**	**PR**	**24**	AE G3	CVP(10), R-THPCOP(6), R-KIC(4), Rituximab(8)

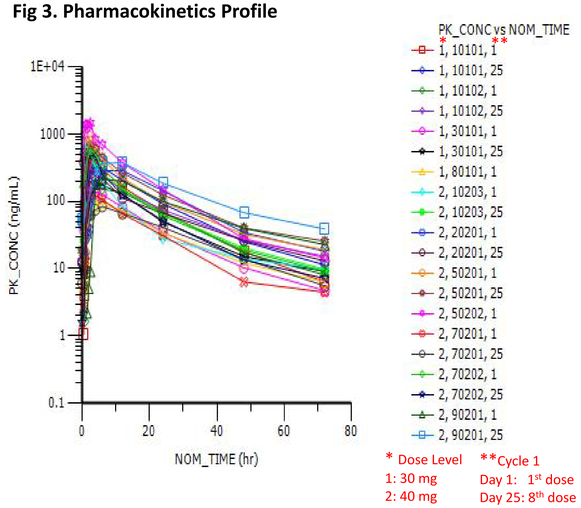
Pharmacokinetics

Preliminary results were available from 10 patients. Inter-patient variability was noted as expected of an oral agent.

Mean half-life ($t_{½}$) was between 16.5 and 20 hours (h) with a T_{max} between 2.5 and 3.5 h. Mean C_{max} and AUC increased with dose (30 mg: 210 ng/mL; 3660 h*ng/mL and 40 mg: 590 ng/mL; 7200 h*ng/mL).

Due to the small sample size and interpatient variability, correlation between PK parameters and clinical findings could not be made. Population PK is planned in ongoing studies.

Fig 3. Pharmacokinetics Profile



* Dose Level
1: 30 mg
2: 40 mg

**Cycle 1
Day 1: 1st dose
Day 25: 8th dose

SUMMARY AND CONCLUSIONS

This phase I trial evaluated the safety profiles of HBI-8000 administered orally at 30 and 40 mg twice weekly. At both doses, HBI-8000 was well tolerated. Observed toxicities were easily managed with supportive care and dose interruptions/reductions. Tumor response in patients who completed at least one cycle of treatment was apparent especially in patients in 40 mg dose cohort. The Data Monitoring Committee and Study Monitoring Committee supported the assessment that the 2 observed DLTs at 40 mg were clinically manageable. Taking into consideration of risk and benefit in R/R NHL, 40 mg BIW was recommended for phase II studies in R/R PTCL and R/R ATL. A registration trial for R/R PTCL is ongoing in Japan with Korean sites pending approval. A registration trial in R/R ATL is ongoing in Japan.

Reference:
Shi Y, Dong M. et al Results from a multicenter, open-label, pivotal Phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. 2015 Annals of Oncology 26: 1766