Delpazolid (LCB01-0371)

Oxazolidinone antibiotic for MDR-TB

2018 WGND Annual Meeting

October 24, 2018

The Hague, The Netherlands

Young Lag Cho
LegoChem Biosciences, Inc., Daejeon, Korea

Contents

- Overview of LegoChem Biosciences
- Key Highlights of Delpazolid
- Physicochemical properties
- Mode of Action
- Activity for MDR-TB
- Phase I study summary
- Ongoing Phase 2a EBA Study Overview
- Conclusion and plan

Company overview : LegoChem Biosciences, Inc.

Leader in novel drug development
with world-class researchers, technology, and global experiences

Who we are?

Company profile

- **Foundeda in May 2006**
- **IPO in May 2013**
- **126 employees (66 in R&D)**

What is Core Competence?

Core Technologies

- ***LegoChemistry*** **: Unique scaffold based new chemical drug discovery**
- ***ConjuAll*** **: Next-generation ADC Platform**

What we have?

Development pipelines

- **Phase II : 1 (Delpazolid)**
- **Phase I finished : 2**
- **IND stage : 3**

Takeda · novimmune · 녹십자 GREEN CROSS · FOSUNPHARMA 复星医药 · SAMSUNG SAMSUNG MEDICAL CENTER · ADDEXAGEN · bridgebio therapeutics · GEOM THERAPEUTICS · ablbio · YBIOLOGICS · R 诺迈西 RMX Biopharma Co.,Ltd

Delpazolid (LCB01-0371) : Key Highlights

Efficacy

- Similar or better in vitro & in vivo activity compared to Linezolid against most of G-positives and mycobacteria
- No cross-resistance and Low resistant rate
- Excellent PK / PD profile (PAE in mouse: 11hr - 16hr)

Safety

- Reduced myelosuppression in animal and human study
  - **No myelosuppression was seen in 21 days repeated phase 1 (MAD) study up to 1200mg BID (2400mg / day)**
- No CYP and QT prolongation issue

PK

- Excellent human bioavailability (BA ~100%, PO / IV switchable)
- No food effect
- Low protein binding (37% in human)
- Fast clearance with no accumulation

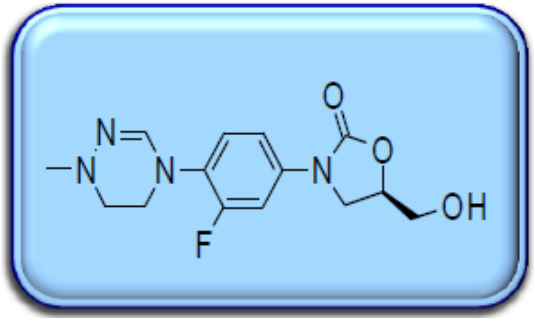
FDA Designation

- **Orphan Drug Designation (ODD)**
- **Qualified Infectious Disease Product (QIDP) designation**
- **Fast Track designation**

Delpazolid: Physicochemical Properties Overview

*Delpazolid is **Safe** and **Potent** 2nd Generation Oxazolidinone Antibiotics*

- **Therapeutic Area** : Infectious disease, Antibacterial
- **Target pathogen** : Gram+ (MRSA, VRE, *S. pneumoniae*), **MDR-TB**
- **Stage** : Phase 2 (PO), Phase 1 (IV)



Physicochemical properties

	Method	LCB01-0371
MW	MS	308.3
mp	DSC	180~181°C
pKa	GLpKa	4.82 ± 0.005
logP	GLpKa	0.19 ± 0.02
Permeability	PAMPA	-6.31 ± 0.06 (grade: medium)

Delpazolid: Mode of Action

Inhibition activity of protein synthesis in bacteria and mitochondria

Compound	Bacteria	Human Mitochondria		Animal Mitochondria (reported)*
	E.coli	K562 cell (cancer cell)	AC16 cell (heart cell)	Rat, Rabbit (liver & heart)
Delpazolid	2.6 uM	4.8 uM	10.9 uM	NA
Linezolid	11.6 uM	3.1 uM	10.0 uM	12.8 uM

- *E. coli : in vitro coupled transcription / translation assay*
- K562 cell: human chronic myelogenous leukemia cell line
- AC16 cell: human cardiomyocyte cell-line

* Ref : E. E. McKee, M. Ferguson, A. T. Bentley, T. A. Marks "Inhibition of Mammalian Mitochondrial Protein Synthesis by Oxazolidinones" Antimicrob Agents Chemother. 2006:50:2042–2049

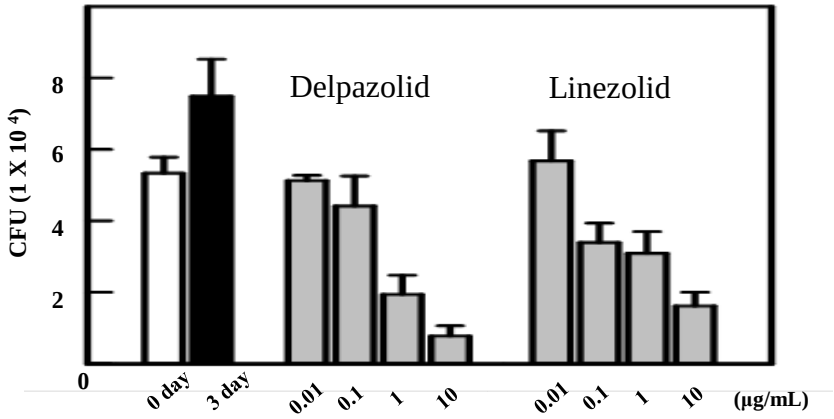
Delpazolid showed **superior activity** compared to Linezolid in prokaryote but **similar mitochondrial protein synthesis inhibition**

Activity for MDR-TB

1. MIC/MBC of MTB (H37Rv)

	MIC (ug/mL)	MBC99 (ug/ml)
Sutezolid	0.125	2
Linezolid	0.5	**>16**
Delpazolid	0.5	**4**

2. Intracellular Survival Assay



3. Reported MIC of MDR-TB (n=120) and XDR-TB (n=120) isolates in China [ref]

	Linezolid	Delpazolid
MDR-TB MIC_{90}	1 ug/mL	0.5 ug/mL
XDR-TB MIC_{90}	0.25 ug/mL	1 ug/mL
ECOFFs (epidemiological cutoff values)	1.0 ug/mL	2.0 ug/mL
Resistant rate of MDR-TB	6.67%	0.83%
Resistant rate of XDR-TB	4.17%	4.2%

*(Ref : Zhaojing Zong et al. "**Comparison of *in vitro* activity and MIC distributions between the novel oxazolidinone delpazolid and linezolid against multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* in China**"
AAC Accepted Manuscript Posted Online 29 May 2018, Antimicrob. Agents Chemother. doi:10.1128/AAC.00165-18)

Phase 1 Study: Summary

Phase 1a SAD

Study design : Double blind, randomized, placebo control, first-in-human design

✓ N=64, 8 subject per group (6 active + 2 placebo)

✓ Doses: 50mg, 100mg, 200mg, 400mg, 800 mg, 1,600 mg, 2,400 mg, 3,200 mg

MTD: 2,400mg (Up to 2,400mg, only mild adverse events were reported)

Phase 1b MAD-7days

Study design : Double blind, randomized, placebo control

✓ N=32, 8 subject per group (6 active + 2 placebo)

✓ Doses: 400 mg, 800 mg, 1,200 mg, 1,600 mg BID for 7 days

MTD: 1,200mg BID (Up to 2,400mg/day, only mild adverse events were reported)

Phase 1b MAD-21days

Study design : Double blind, randomized, placebo control

✓ N=36, 12 subject per group (10 active + 2 placebo)

✓ Doses: 800 mg QD and BID, 1,200 mg BID for 21 days

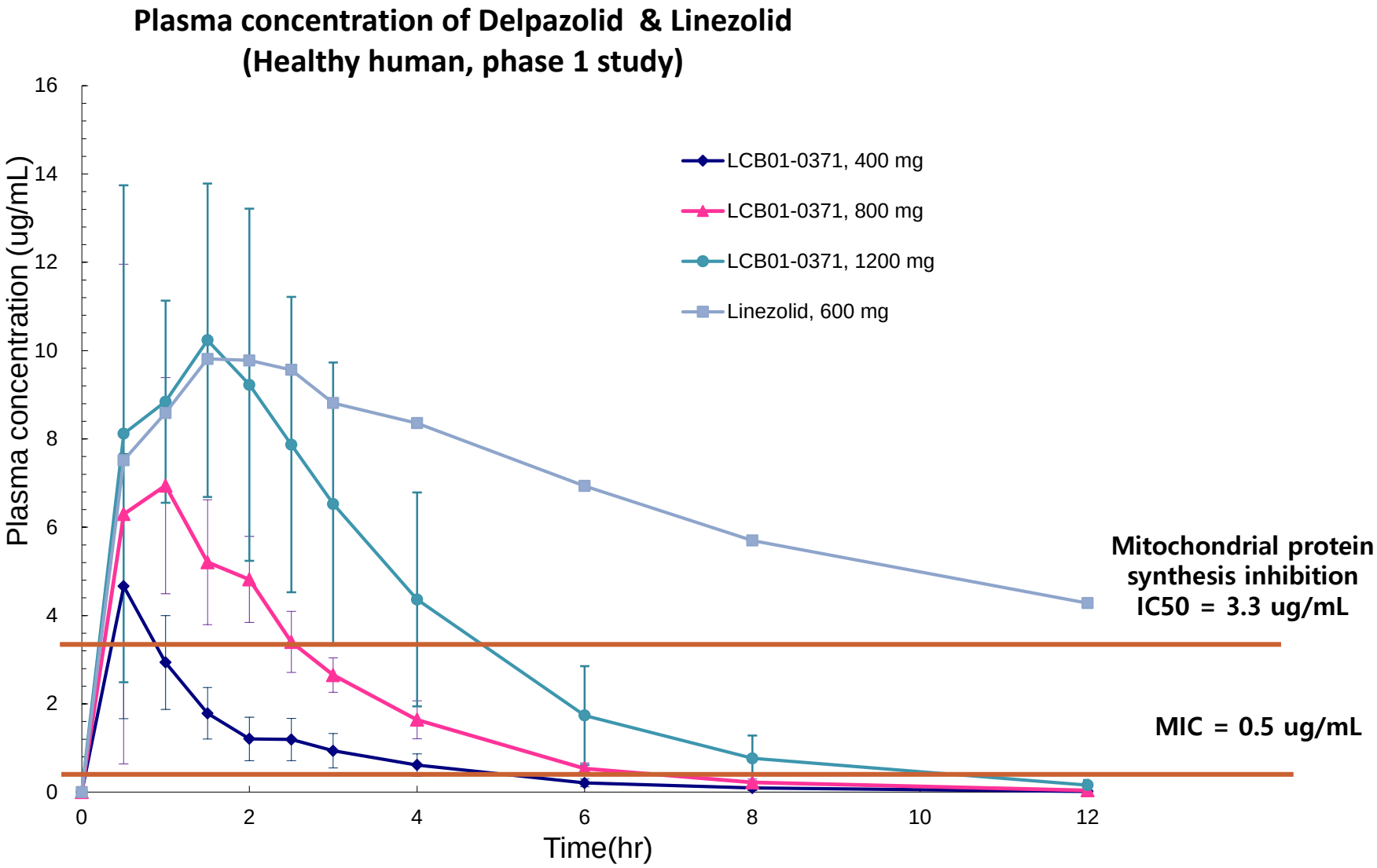
MTD: 1,200mg BID (Up to 2,400mg/day, No SAE reported)

PK of LCB01-0371 in human_MAD 7day

- **PK parameter of LCB01-0371 at the Day1 in multiple-dose study**

PK parameter	400 mg	800 mg	1200 mg
Cmax (ug/ml)	5.62 (2.39)	11.15 (5.88)	13.83 (2.07)
Tmax (hr)	0.60 (0.14)	1.04 (0.75)	1.13 (0.63)
$T_{1/2}$ (hr)	1.56 (0.07)	1.58 (0.17)	1.69 (0.17)
AUC_{tau} (ug*hr/ml)	7.79 (2.96)	19.46 (4.38)	38.15 (14.22)
$AUC_{0\text{-}inf}$ (ug*hr/ml)	7.83 (2.99)	19.56 (4.44)	38.56 (14.52)
Accumulation ratio (D7AUC/D1AUC)	1.13 (0.12)	1.47 (0.44)	1.11 (0.20)
Vz_F (l/kg)	2.02 (0.93)	1.49 (0.31)	1.28 (0.37)
Cl_F (l/hr/kg)	0.91 (0.42)	0.66 (0.17)	0.54 (0.19)
MRTlast (hr)	2.23 (0.20)	2.37 (0.29)	2.90 (0.43)
Cmax_norm(kg/l)	0.91 (0.39)	0.91 (0.48)	0.75 (0.11)
$AUC_{0\text{-}inf}$_norm(kg*hr/l)	1.27 (0.49)	1.59 (0.36)	2.09 (0.79)

Why Delpazolid is safer than Linezolid?



Fast clearance rate of Delpazolid may relieve the mitochondrial toxicity

Delpazolid: EBA Study Overview

Outline of the ongoing Ph2a trial in Korea (Drug Susceptible Pulmonary Tuberculosis)

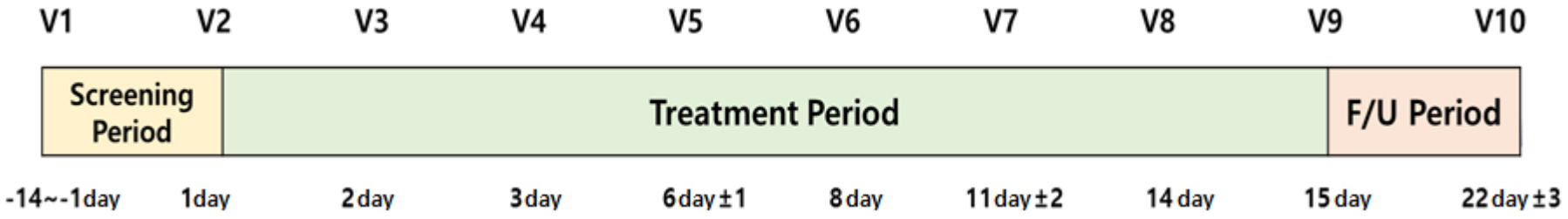
	Description
Sites and Country	13 sites in Korea
Planed	≥ 80
Treatment Period	2 weeks (14 days)
EBA analysis by	Korea Institute of Tuberculosis (KIT)
Primary endpoint	CFU count (solid culture)
Safety parameters	Laboratory, EKG, AEs, Vital sign
Pharmacokinetics	Pop PK

Delpazolid: EBA Study Overview

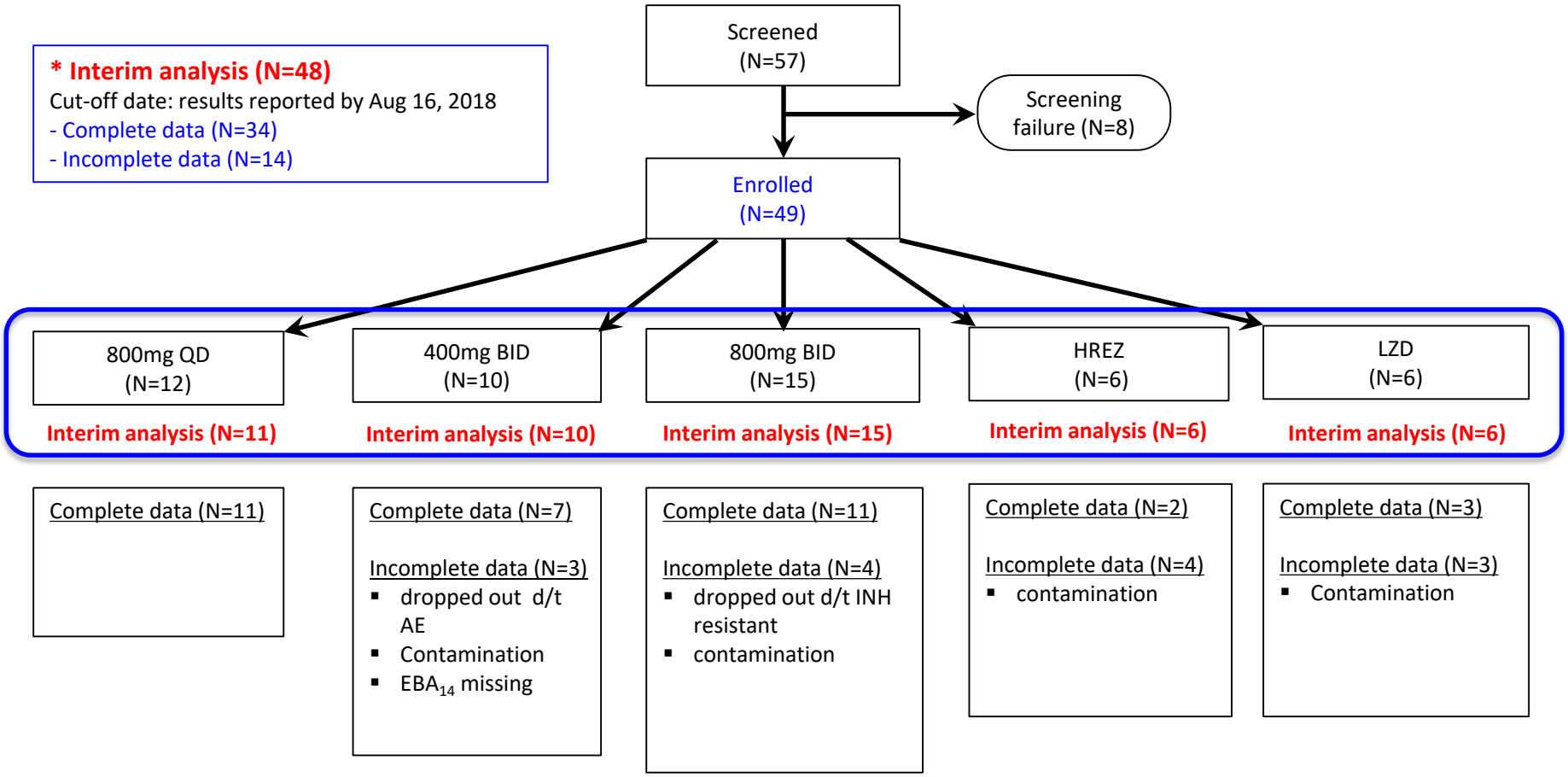
- Title
  - A Prospective, Randomized, Open, Active-controlled, Multi-center, Interventional, Exploratory, Phase II Trial to Evaluate the Early Bactericidal Activities (EBA), Safety and Pharmacokinetics of Orally Administered LCB01-0371 in Adult Patients With Smear-Positive Pulmonary Tuberculosis

- Primary Endpoint
  - $EBA_{0\text{-}14}$
    - EBA(CFU) day 0-14=(log10CFU on day 14 - log10CFU on day 0)/(14-0)

	Delpazolid (800mg/QD)	Delpazolid (400mg/BID)	Delpazolid (800mg/BID)	Delpazolid (1200mg/QD)	HREZ	Linezolid	Total
N	16	16	16	16	8	8	80



Patient disposition & Data analysis set: Interim analysis (N=48)



* Delpazolid 1200mg QD group was added recently and not enrolled yet

Baseline characteristics (N=48)

Variable		Number
Age (yr)	mean (±sd)	51.6 (±9.8%)
Gender	Male	40
	Female	8
ADM/OPD	ADM	32
	OPD	16
Medical history	Yes	35
	No	13
	DM	15
	HTN	7
First TB diagnosed	Yes	41
	No	7
Completeness of data	Complete	34
	Incomplete	14

Variable		Number
INH-R	S	48
	R	0
Cavity	Cavity (-)	12
	Cavity (+)	36
Bilateral lesions on CXR	Unilateral	27
	Bilateral	21
CDC smear score	1+	15
	2+	7
	3+	9
	4+	17
Randomized group	HREZ	6
	LZD	6
	800 bid	15
	400 bid	10
	800 qd	11

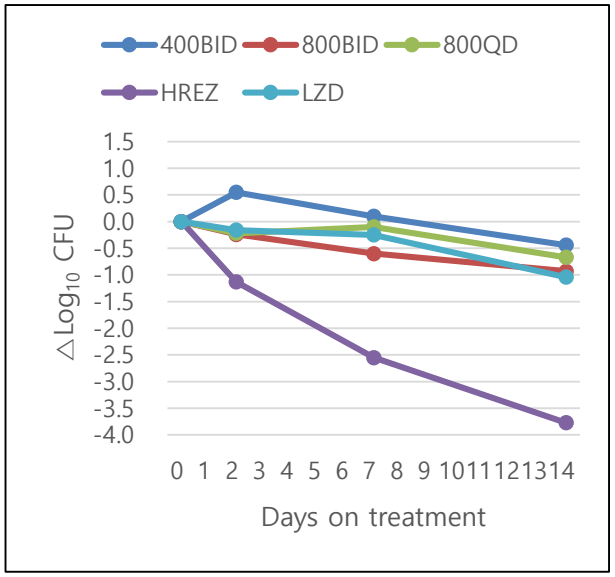
Delpazolid: Phase 2a EBA Study Overview

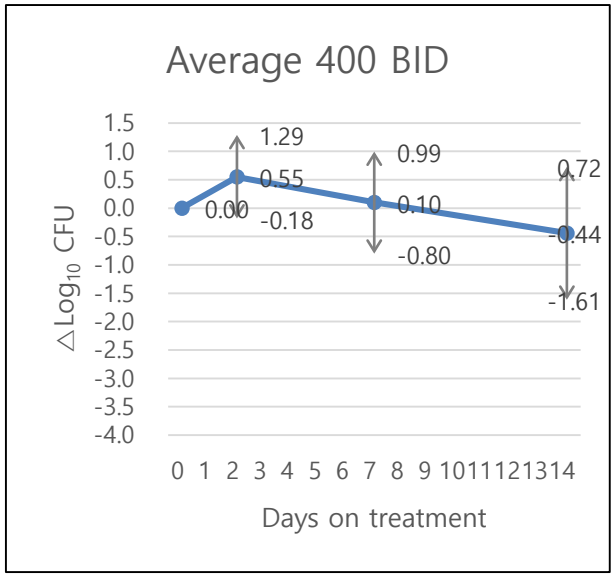
Sputum cfu count results (N=48)

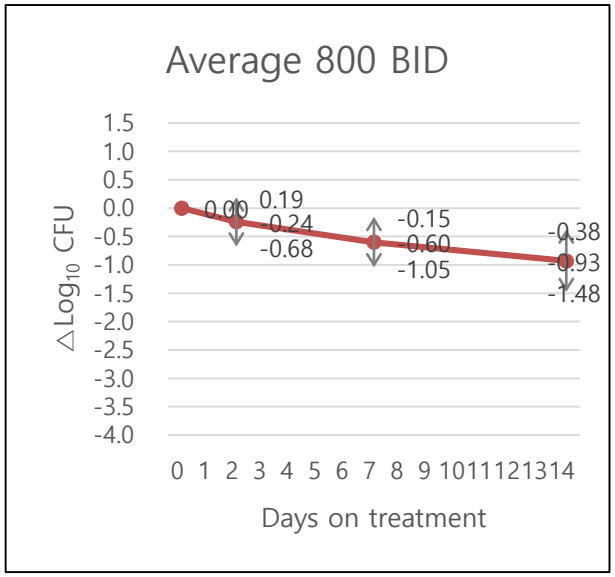
	Delpazolid												Linezolid				HREZ			
	400 mg BID (800 mg/day)				800 mg QD (800 mg/day)				800 mg BID (1600 mg/day)				600 mg BID (1200 mg/day)							
	N=10				N=11				N=15				N=6				N=6			
	n	mean	95% CI		n	mean	95% CI		n	mean	95% CI		n	mean	95% CI		n	mean	95% CI	
log CFU/ml)																				
Baseline	9	5.75	4.65	6.84	11	5.02	4.26	5.77	14	5.52	4.64	6.40	6	6.28	5.40	7.16	4	4.51	2.28	6.74
Day 2	8	5.89	5.27	6.50	11	4.80	3.92	5.67	15	5.24	4.42	6.07	6	5.67	4.52	6.81	6	4.08	2.80	5.35
Day 7	8	5.52	4.79	6.25	11	4.92	4.19	5.65	13	5.11	4.18	6.04	6	4.51	2.28	6.74	5	3.31	2.03	4.60
Day 14	7	4.74	3.65	5.84	11	4.35	3.53	5.17	12	4.77	3.86	5.67	3	5.37	2.98	7.76	2	1.77	-8.59	12.13
EBA (Δlog CFU/mL)																				
Day 0-2	8	0.42	-0.28	1.11	11	-0.22	-0.60	0.16	14	-0.11	-0.48	0.26	6	-0.61	-1.32	0.10	4	-0.55	-2.13	1.03
Day 0-7	8	0.05	-0.71	0.81	11	-0.10	-0.65	0.46	12	-0.50	-0.96	-0.03	6	-1.77	-3.63	0.09	3	-1.43	-6.25	3.39
Day 2-14	7	-1.00	-1.70	-0.30	11	-0.45	-1.06	0.17	12	-0.70	-1.14	-0.26	3	-0.88	-2.11	0.35	2	-2.64	-35.63	30.35
Day 0-14	7	**-0.44**	-1.61	0.72	11	**-0.67**	-1.16	-0.17	11	**-0.93**	-1.48	-0.38	3	**-1.04**	-2.16	0.09	2	**-3.77**	-25.48	17.94

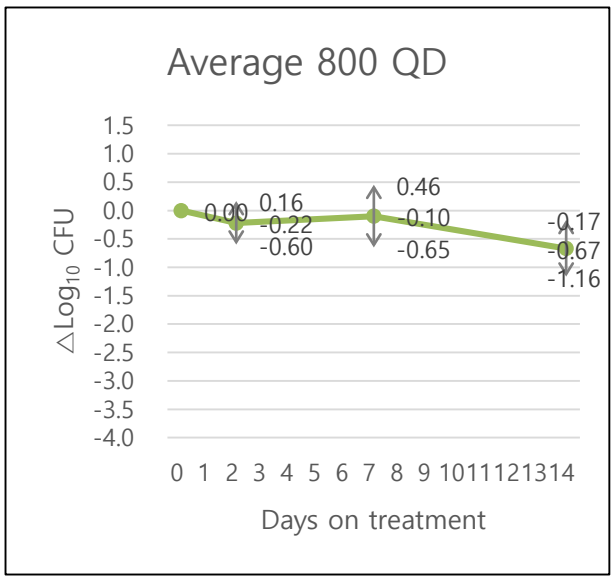
Delpazolid: Phase 2a EBA Study Overview

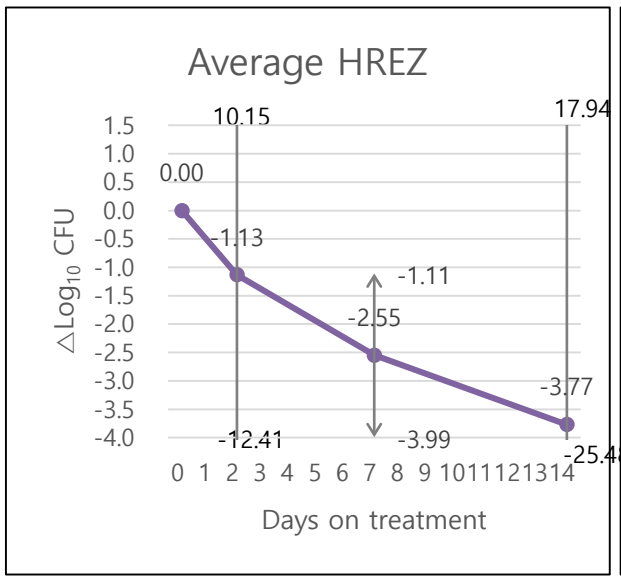
95% Confidence interval

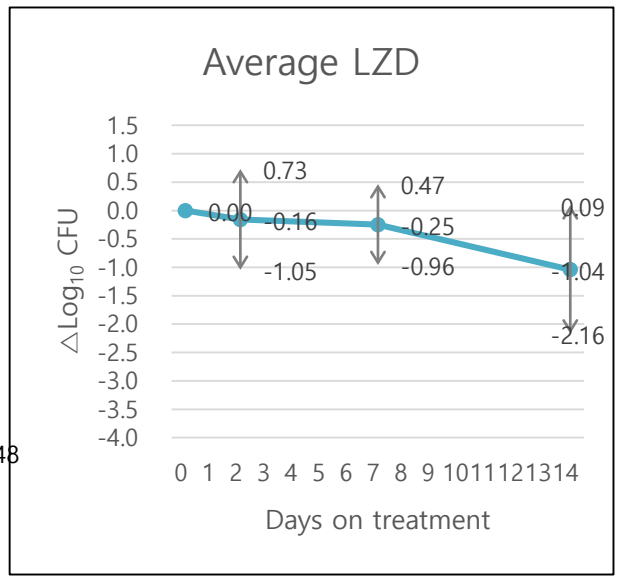






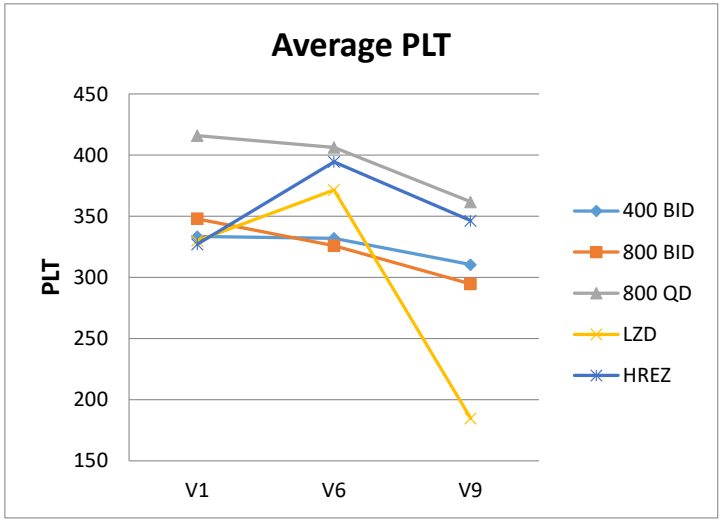


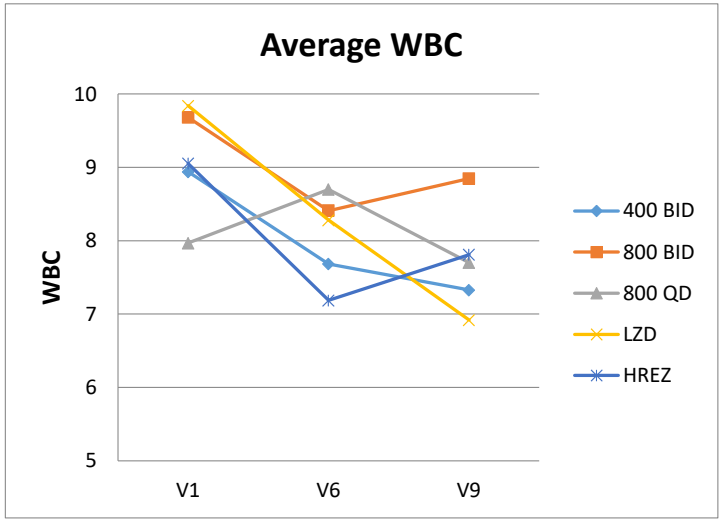


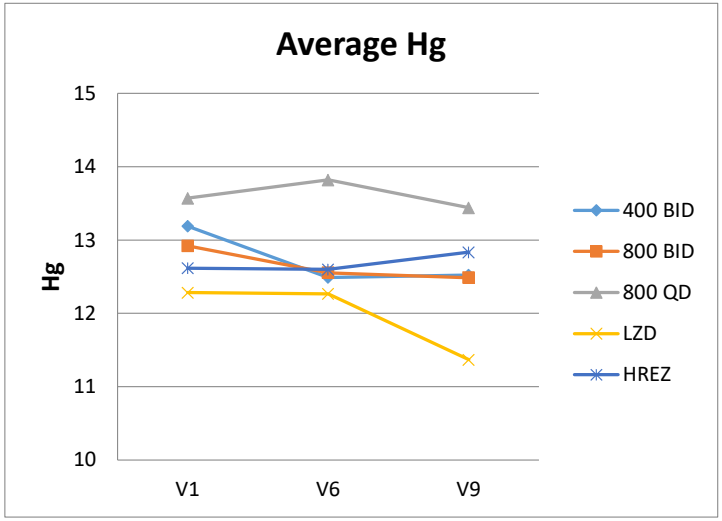


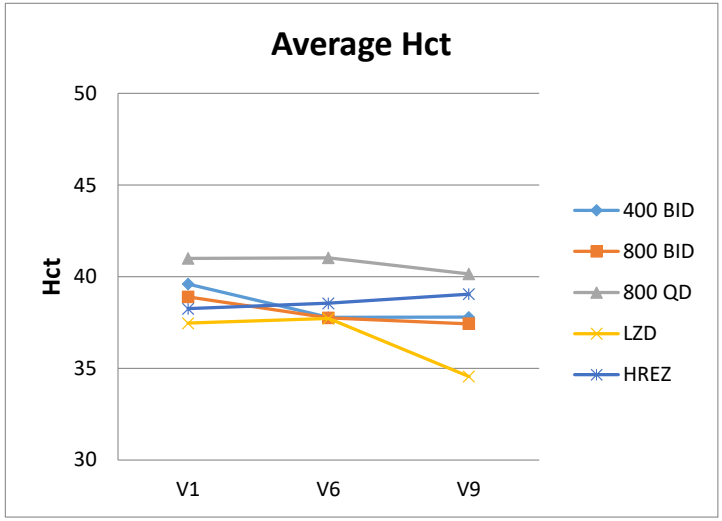
Delpazolid: Phase 2a EBA Study Overview

Laboratory Data









Delpazolid: Phase 2a EBA Study Overview

Drug Related Adverse Events by Dose group (N=48)

Adverse events	400mg BID (N=10)	800mg QD (N=11)	800mg BID (N=15)	LZD 600mg BID (N=6)	HREZ (N=6)	Total (N=48)
	n(N)	n(N)	n(N)	n(N)	n(N)	
Acute diarrhea	1(1)					1(1)
Anorexia	1(1)					1(1)
Diarrhea			1(1)			1(1)
Dizziness	1(1)					1(1)
Epigastric pain					1(1)	1(1)
Fever				2(2)		2(2)
Hepatotoxicity				1(1)		1(1)
Myalgia	1(1)					1(1)
Nausea	1(1)			2(2)	2(2)	5(5)
Paresthesia					1(1)	1(1)
Vomiting				1(1)		1(1)
Total	5(5)	0(0)	1(1)	6(6)	4(4)	16(16)

†**n: Number of subjects with adverse events; N: Number of adverse events**

Conclusion and Plan

EBA study Interim analysis :

- Delpazolid 800 mg showed 7~8 times lower AUC than Linezolid 600mg (19 vs. 144 ug*Hr/mL) but similar EBA_{0-14} was seen in BID treatment
- 800 mg QD showed better extended EBA than 400 mg BID (800mg/day)

➢ 1200 mg QD and 800 mg BID group will be evaluated for 6 months safety and efficacy in next clinical study

Acknowledgement

- **Tae Sun Shim (Asan Medical center)**
- Won Joong Ko (Samsung Medical Center)
- Seung Joon Kim (The Catholic University of Korea, Seoul ST. Mary's Hospital)
- Ee Hyung Kim (Kyung Hee University Hospital at Gangdong)
- Min Kwang Byun (GangnamSeveranceHospital)
- Yong Bum Park (Kangdong Sacred Heart Hospital)
- Joon Sung Joh (National Medical Center)
- Sang Haak Lee (The Catholic University of Korea, ST. Paul's Hospital)
- Ju Sang Kim (The Catholic University of Korea, Incheon ST. Mary's Hospital)
- Jin Woo Kim (The Catholic University of Korea, Uijeongbu ST. Mary's Hospital)
- Tae Hyung Kim (Hanyang University Guri Hospital)
- Jeong Ha Mok (Pusan National University Hospital)
- Soo Hyun Bae(Ulsan University Hospital)
- Yong Hyun Kim (The Catholic University of Korea, Bucheon ST. Mary's Hospital)
- Sung Kyoung Kim(The Catholic University of Korea, ST. Vincent's Hospital)
- Jin Young Oh (Dongguk University Medical Center)

- Hong Jo Choi (Korea Institute Tuberculosis)
- Hyeong Seok Lim (Asan Medical center)
- Hye Young Lee(Yonsei college of Health Science)

This research is supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI17C1234).