BBT-877, a Potent Autotaxin Inhibitor in Clinical Development to Treat Idiopathic Pulmonary Fibrosis

PA1293
ERS2019

Gwanghee Lee[1], Sang Uk Kang[1], Jeong-Hyun Ryou[1], Jong-Jin Lim[1], Yong-Hee Lee[1]
[1]Full-time employee of Bridge Biotherapeutics, Seongnam, Republic of Korea

bridgebio therapeutics

ABSTRACT

Idiopathic Pulmonary Fibrosis (IPF) is a progressive, irreversible and fatal lung disease with unmet medical needs. Autotaxin (ATX) is an extracellular enzyme involved in the generation of lysophosphatidic acid (LPA). Preclinical and clinical data have suggested the ATX – LPA – LPA receptor (LPAR) axis plays a pivotal role in the pathogenesis and the progression of IPF.

BBT-877 is an orally available small molecule inhibitor against ATX. In ex vivo enzymatic assays using human plasma, IC50 of BBT-877 was measured 6.5 – 6.9 nM (LPA 18:2) whereas that of GLPG1690 was measured 75 – 132 nM. To determine in vivo anti-fibrotic efficacy of BBT-877, bleomycin was intranasally administrated in mice at day 0, and BBT-877 was administrated orally twice a day from day 7 to 21. The BBT-877 treatment showed anti-fibrotic efficacy as revealed by significantly reduced body weight loss, lung weight and Ashcroft score as well as collagen content compared to the vehicle-treated group.

During phase 1 clinical trial with 80 healthy volunteers, in which 50 – 800 mg (SAD) and 200 – 800 mg QD or 100 – 200 mg BID for two weeks (MAD) doses were administrated, all dose levels were safe and well tolerated with no SAEs. Pharmacokinetic analysis revealed the dose-proportional increase in systemic exposure with elimination half-life of approximately 12hr. The decrease of plasma LPA level was maintained at 80% or higher for 24hr when 400 mg/day or higher dose of BBT-877 was administrated.

Taken together, nonclinical data suggest BBT-877 is a potent, selective, and potentially best-in-class ATX inhibitor. Phase 1 clinical data demonstrate BBT-877 is a safe and well-tolerated drug with excellent pharmacokinetic-pharmacodynamic profiles.

RESULTS

Table 1. Inhibitory potency of BBT-877 to inhibit enzyme activity in vitro

Compound	IC_{50} (nM)
BBT-877	2.4
GLPG1690	5.0
PAT-505	>100

Table 2. Ex vivo LysoPLD activity assay using mouse plasma

Compound	IC_{50} (nM)				
	LPA 16:0	LPA 18:0	LPA 18:1	LPA 18:2	LPA 20:4
BBT-877	3.3	16.9	8.3	5.3	5.4
GLPG1690	-	-	36.4	-	-

Table 3. Ex vivo LysoPLD activity assay using human plasma

Compound	IC_{50} (nM)				
	LPA 16:0	LPA 18:0	LPA 18:1	LPA 18:2	LPA 20:4
BBT-877	6.2	8.4	7.7	6.9	8.8
GLPG1690	102	149	133	132	150
PAT-505	36.9	92.6	70.5	66.4	56.9

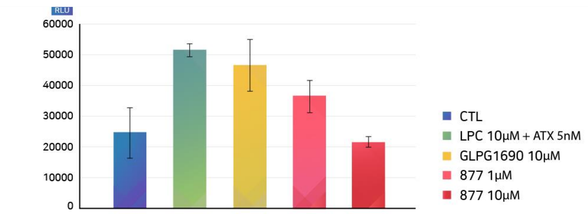

Figure 1. In vitro chemostasis assay

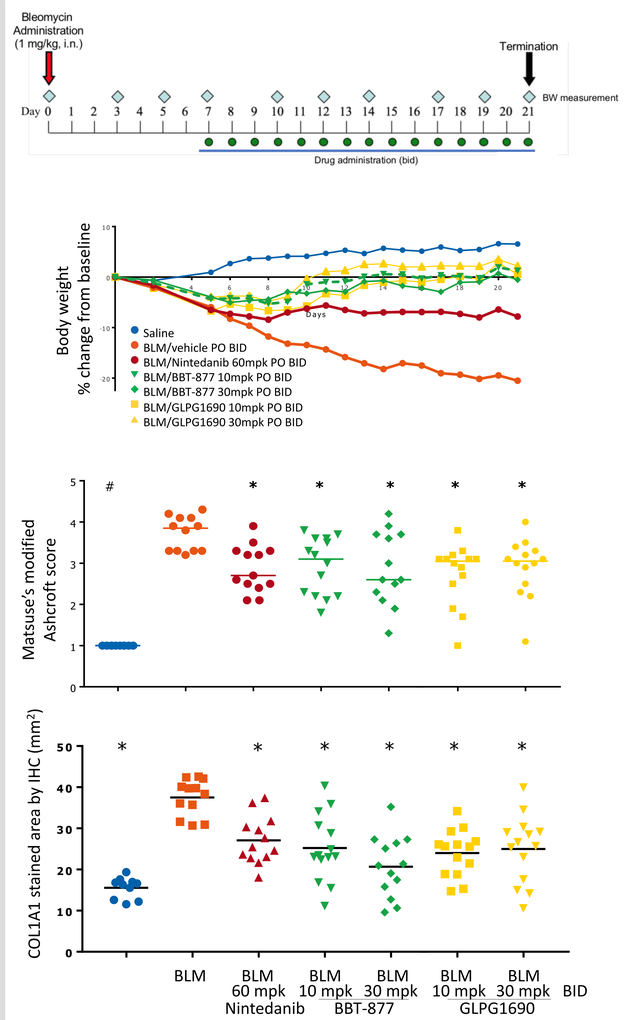

Figure2. BLM-induced IPF mouse model

Table 4. In vitro cytotoxicity assay

Compound	Cell types and CC_{50} (uM)			
	HepG2 (hepatocellular carcinoma cell)	CHO-K1 (Chinese hamster ovary cell)	CCD-8Lu (normal lung fibroblast)	FA2N4 (immortalized human hepatocyte)
Pirfenidone	> 100	> 100		
Nintedanib	2.7	8.0	9.0	5.8
GLPG1690	9.4	36.9	5.8	36.5
PAT-505	> 100	95.0	> 100	5.4
BBT-877	> 100	> 100	> 100	> 100

Phase 1 Clinical Trial

- Randomized, double-blind, placebo-controlled, single center, dose range study
- Total 80 healthy subjects
- Single ascending dose: 5 cohorts
- Multiple ascending dose: 14 days, 5 cohorts
  - 3 cohorts for QD
  - 2 cohorts for BID
- Safety parameters: AEs, ECG, vital signs, laboratory biochemical/hematology, and urinalysis
- PK: BBT-877 plasma and urine concentrations determined by LC-MS/MS
- PD marker
  - Plasma LPA (18:2, 20:4) determined by LC-MS/MS

Table 5. PK data of BBT-877 in healthy volunteers

Cohort	T_{max}	C_{max}	AUC_{last}	Half-life
Cohort 1 (50 mg)	2.3	670	3225	12.1
Cohort 2 (100 mg)	3	1119	5368	12.6
Cohort 3 (200 mg)	2.5	2725	12985	15.2
Cohort 4 (400 mg)	2	6195	32659	10.0
Cohort 5 (800 mg)	3.5	10568	60118	11.7
Cohort 6 (200 mg QD)	5	1207	7851	14.7
Cohort 7 (400 mg QD)	7	1590	12870	13.3
Cohort 8 (800 mg QD)	5	4024	30096	9.7
Cohort 9 (100 mg BID)	3.5	655	4899	12.3
Cohort 10 (200 mg BID)	7.5	1080	11866	8.4

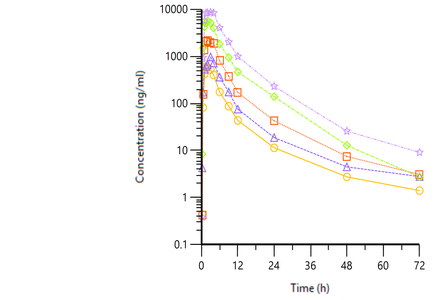

Figure 3. Plasma concentrations (SAD) of BBT-877 in Phase 1 trial.

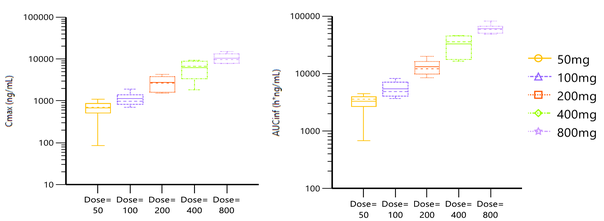

Figure 4. C_{max} and AUC (SAD) of BBT-877 in Phase 1 trial.

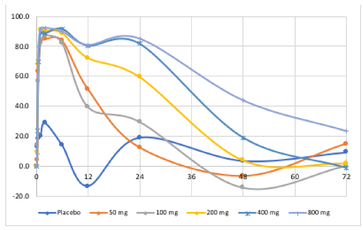

Figure 5. LPA inhibitions (SAD) of BBT-877 in Phase 1 trial.

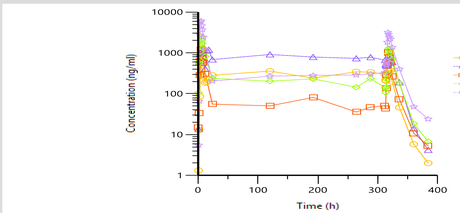

Figure 6. Plasma concentrations (MAD) of BBT-877 in Phase 1 trial.

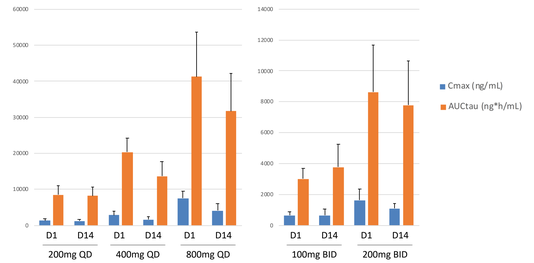

Figure 7. C_{max} and AUC_{tau} (MAD, D1 vs D14) of BBT-877 in Phase 1 trial.

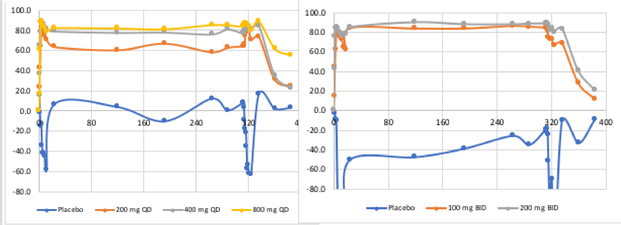

Figure 8. LPA inhibitions (MAD) of BBT-877 in Phase 1 trial.

Safety result:
- All SAD/MAD doses (10 cohorts) were safe and well tolerated with no SAEs.
- There were no clinically related finding in ECGs, vital signs, and laboratory parameters.

PK result:
- Dose proportional AUC and C_{max}
- Median T_{max} was 2-3 hours; mean $t_{1/2}$ was approximately 12 hours
- Steady-state has been reached by Day 6

PD result:
- Dose related increase of % inhibition
- LPA inhibition was >80% at steady state trough at 800 mg QD, 100, 200 mg BID.

CONCLUSION

1. BBT-877 is an orally available drug candidate for IPF treatment.
2. BBT-877 targets ATX, which is preclinically and clinically validated.
3. BBT-877 provides the best-in-class potential from safety and efficacy viewpoints.
4. Currently, chronic GLP toxicology and DART studies are ongoing.
5. Phase 1 is being conducted in USA and Phase 2 will be initiated in 2020 as multi-regional clinical trial.
6. The predicted human effective dose is in the range of 100-200 mg BID. Phase 1 PK/PD data (LPA) supports consideration of QD dosing.

**Licensing deal with Boehringer Ingelheim (BI) closed July 16, 2019. Clinical development beyond Phase 1 is conducted by BI.*