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

12237
ATS2019

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ABSTRACT

RATIONALE
Idiopathic Pulmonary Fibrosis (IPF) is a progressive, irreversible and fatal lung disease. Its risk factors include age, genetic and environmental/occupational factors. Currently available therapies only slow down disease progression. Autotaxin (ATX) is an extracellular enzyme involved in the hydrolysis of lysophosphatidylcholine (LPC) to form lysophosphatidic acid (LPA). The ATX – LPA – LPA receptor (LPAR) axis has been suggested to play a pivotal role in the pathogenesis and the progression of IPF. Genetic deletion of ATX, LPAR1 and LPAR2 significantly improved the severity of bleomycin-induced pulmonary fibrosis in mouse. Pharmacological inhibition of ATX and LPAR1 reduced lung fibrosis parameters resulted from the bleomycin treatment in mouse. Positive efficacy data were obtained from clinical trials with drugs targeting the ATX – LPAR pathway.

METHODS
The inhibitory potency of BBT-877, an orally available small molecule inhibitor of ATX, was measured by FS-3 (in vitro) and plasma LPC (ex vivo) assays. Transwell cell migration assay was used to quantify in vitro anti-migratory efficacy of BBT-877. In mouse disease model, bleomycin was intranasally administrated to induce pulmonary fibrosis at day 0, and BBT-877 was given orally twice a day from day 7 to 21.

RESULTS
In vitro and ex vivo IC_{50} of BBT-877 were determined to be 2.4 nM and 6.89 nM (LPA 18:2), respectively. LPA-induced cell migration was effectively inhibited by BBT-877. In vivo anti-fibrotic efficacy of BBT-877 was shown in the mouse model of bleomycin-induced pulmonary fibrosis. BBT-877 did not significantly impair the viability of various cell types even when treated at high concentrations (CC_{50}: >100 μM). IND-enabling toxicology studies have been completed in the rat and monkey models, with demonstrated good safety profiles and no remarkable findings up to 1000 and 300 mg/kg/day, respectively.

CONCLUSION
Results of comprehensive in vitro and in vivo studies with BBT-877 demonstrate this compound is a very potent, selective, potentially best-in-class ATX inhibitor with a very favorable safety profile and support further investigation in clinical testing for the treatment of IPF. Phase 1 clinical studies are currently ongoing and will be completed by Aug 2019.

RESULTS

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

Compound	IC_{50} (nM)
BBT-877	2.4
GLPG1690	4.99
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	3.33	16.9	8.28	5.31	5.36
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	6.19	8.35	7.66	6.89	8.76
GLPG1690	102	149	133	132	150
PAT-505	36.9	92.6	70.5	66.4	56.9

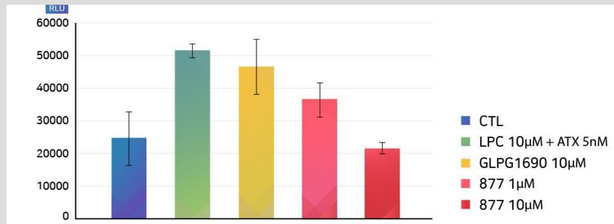

Figure 1. In vitro chemostasis assay

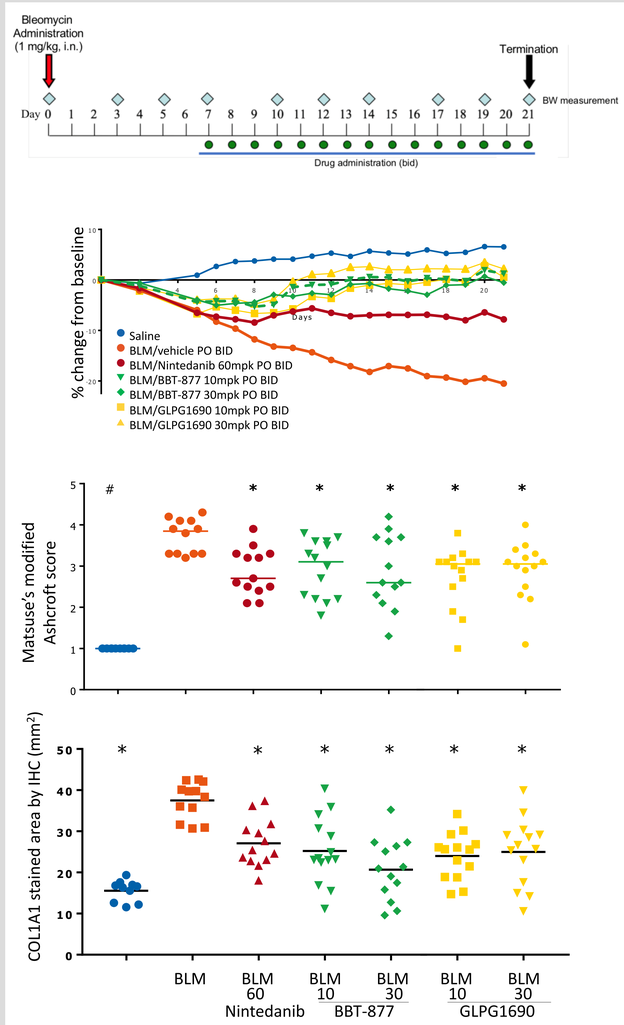

Figure2. BLM-induced IPF mouse model

Table 4. PK data of BBT-877 in various animal species

Compound	Mice	Rats	Dogs	Monkeys
IV Dose (mg/kg)	**10**	**10**	**10**	**10**
App $t_{1/2}$ (hr)	3.73	3.88	5.51	6.35
CL (mL/min/kg)	29.7	21.0	7.01	9.68
V_{dss} (mL/kg)	1130	776	691	885
PO Dose (mg/kg)	**10, 30**	**10, 30**	**10, 30**	**10, 30**
AUC range (μg.hr/mL)	1.9, 8.8	4.4, 9.3	7.9, 10.4	9.0, 34.6
Cmax range (μg/mL)	2.3, 4.1	3.5, 3.4	3.0, 3.9	3.3, 13.6
BA range (%)	35, 53	56, 39	36, 16	49, 63

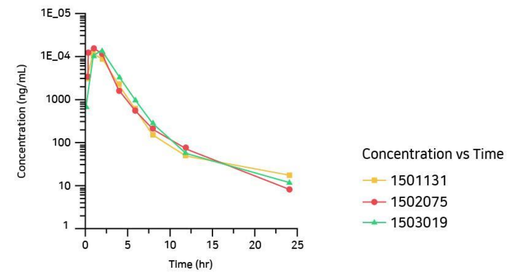

Figure 3. Plasma concentrations of BBT-877 in monkeys at 30 mg/kg

Table 5. In vitro cytotoxicity assay

Compound	Cell types and CC50 (uM)			
	HepG2 (hepatocellular carcinoma cell)	CHO-K1 (Chinese hamster ovary cell)	CCD-8Lu (normal lung fibroblast)	FA2N4 (immortalized human hepatocyte)
Pirfenidone	> 100	> 100		
Nintedanib	2.65	8.02	9.009	5.804
GLPG1690	9.39	36.9	5.794	36.457
PAT-505	> 100	94.965	> 100	5.411
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

SAD 5 Cohorts were completed (May 12).
MAD Cohort 1 (QD) is ongoing.

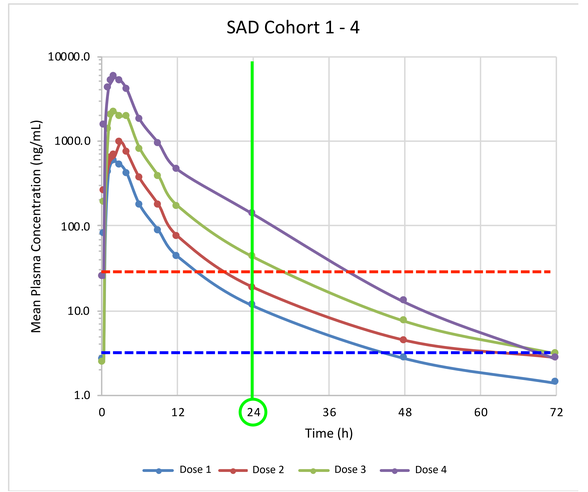

Figure 4. Plasma concentrations of BBT-877 in Phase 1 trial.

Figure 5. C_{max} and AUC of BBT-877 in Phase 1 trial.

PK result:
- Approximate dose-proportional increase in systemic exposure.
- 3rd cohort single dose: plasma concentration was higher than *Ex vivo* IC_{90} for 24 hours.

Safety result:
- All SAD doses (5 cohorts) were safe and well tolerated with no SAEs. All AEs were mild.
- There were no clinically related finding in ECGs, vital signs, and laboratory parameters.

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.
   - Excellent safety (HED of NOAEL at 4w Tox studies: ~ 6 gram)
   - Can achieve > IC_{90} plasma concentration at 24h post-administration
4. Currently, chronic GLP toxicology and DART studies are ongoing.
5. Phase 1 is being conducted in USA and Phase 2 will be initiated early 2020 in multiple countries including USA, Canada, Europe, Asia and Australia.

Disclosed at ATS 2019