BBP-671, a Potential First-in-Class, Potent, Allosteric Modulator of Human Pantothenate Kinases, Is Well-Tolerated and Demonstrates Target Engagement in Healthy Volunteers

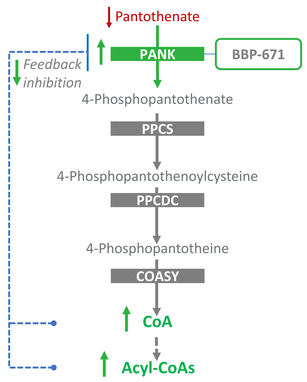
Rajaa Sukhun, PhD[1], Satish Rao, PhD[1], Mallory Harden, PhD[1], Anna Wade, PhD[1], Chris Henry, PhD[1], Agnieszka Jurecka, MD, PhD[1], Daniel Gretler, MD[1], Uma Sinha, PhD[1]

[1]CoA Therapeutics, a BridgeBio company, San Francisco, CA

Background

BBP-671 belongs to a class of small molecules called pantazines, which act as allosteric pantothenate kinase (PanK) modulators. Oral administration of pantazines yielded therapeutic effects in a *SynCre+ Pank1,2* neuronal knockout mouse model of brain CoA deficiency including increased coenzyme-A (CoA) levels in liver and brain, improved weight and locomotor activity, and enhanced life span (Sharma et al., 2018). Additionally, BBP-671 treatment restored glutamate/glutamine levels in the brains of the knockout mice to wildtype levels (Li et al., 2022).

As an activator of human PanK isoforms PanK1, 2, and 3, BBP-671 is anticipated to compensate for the loss of PanK2 in pantothenate kinase-associated neurodegeneration (PKAN), which is a rare, autosomal recessive, neurodegenerative disorder caused by mutations in *PANK2*. BBP-671 is also being developed as a potential therapy for propionic and methylmalonic acidemia, inborn errors of metabolism associated with CoA deficiency.



PanK activation by BBP-671 is expected to increase acyl-CoAs (products of CoA biosynthesis), including acetyl-CoA, and reduce pantothenate (substrate for CoA biosynthesis).

Primary Objective

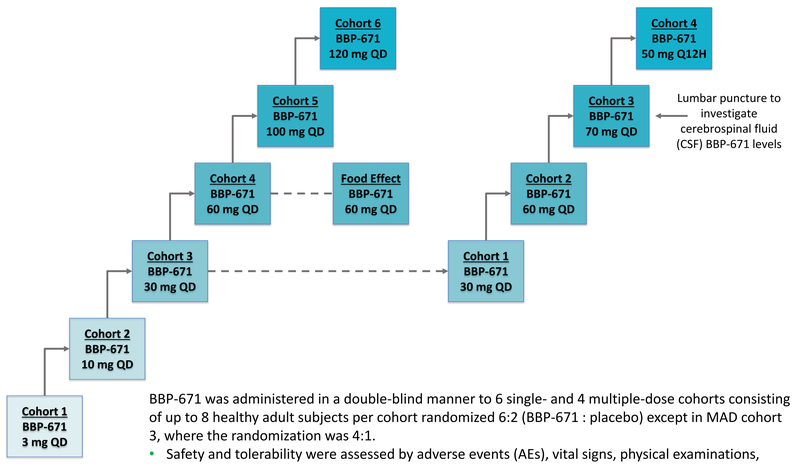
- To evaluate the safety, tolerability, and pharmacokinetics (PK) of single and multiple doses of BBP-671 administered to healthy adult subjects

Secondary Objectives

- To characterize the effect of food on the PK of a single dose of BBP-671
- To demonstrate target engagement of BBP-671 by assessment of whole blood acetyl-CoA and plasma pantothenate concentrations

Study Design & Methods

Single Ascending Dose (SAD) | **Multiple Ascending Dose (MAD)**



BBP-671 was administered in a double-blind manner to 6 single- and 4 multiple-dose cohorts consisting of up to 8 healthy adult subjects per cohort randomized 6:2 (BBP-671 : placebo) except in MAD cohort 3, where the randomization was 4:1.

- Safety and tolerability were assessed by adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECG), and routine safety laboratory tests.
- PK was measured in plasma and cerebrospinal fluid (CSF) using validated bioanalytical (LC-MS/MS) assays.

Key Inclusion Criteria

- 18 to 55 years of age with a body mass index (BMI) of 18 to 32 kg/m^2
- absolute neutrophil count (ANC) ≥2500 × 10^9/L (added after MAD cohort 2, applicable for MAD 3+)

Key Exclusion Criteria

- Recent use of prescription drugs or over-the-counter medications
- Most recent COVID-19 vaccine dose (or booster) must be at least 14 days prior to first dose of study drug
- Clinically relevant history or presence of prespecified medical conditions
- Clinically significant ECG abnormalities at screening

Safety

Single Ascending Dose	Placebo (N=10)	3 mg (N=6)	10 mg (N=6)	30 mg (N=6)	60 mg food effect (N=8)	100 mg (N=6)	120 mg (N=6)
Subjects with SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subjects with Treatment-Related TEAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (25%)*	0 (0%)	1 (17%)*

**treatment-related TEAEs in the SAD cohorts included headache, abdominal pain, and nausea*

Multiple Ascending Dose	Placebo (N=7)	30 mg QD (N=6)	60 mg QD (N=6)	70 mg QD (N=4)	50 mg, Q12H* (N=6)
Subjects with SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subjects with Treatment-Related TEAEs	0 (0%)	0 (0%)	1 (17%)*	0 (0%)	2 (33%)*

**treatment-related TEAEs in the MAD cohorts included neutropenia*

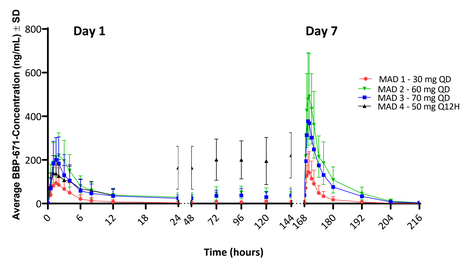
- No Serious Adverse Events (SAEs) were observed with BBP-671 treatment.
- Mild Treatment-Related Treatment Emergent Adverse Events (TEAEs) included headache, abdominal pain, and nausea (5%, 1.7%, and 1.7%, respectively, of all BBP-671-treated subjects).
- Asymptomatic neutropenia was observed in 3 subjects of 22 with repeat dosing of BBP-671. All returned to within normal limits within a few days without any sequelae upon cessation of therapy. There was no apparent association of neutropenia with higher BBP-671 exposures.
- ANC nadirs for subjects who experienced neutropenia in the MAD cohort were 740/µL with 60 mg of BBP-671 once daily, and 750/µL and 1,320/µL with 50 mg of BBP-671 twice daily.

Pharmacokinetics of BBP-671

Parameter	Statistic	Day 1 30 mg QD (N=6)	Day 7 30 mg QD (N=6)	Day 1 60 mg QD (N=6)	Day 7 60 mg QD (N=6)	Day 1 70 mg QD (N=4)	Day 7 70 mg QD (N=4)	Day 1 50 mg Q12H (N=6)	Day 7 50 mg Q12H
AUC_{tau}[a] (ng*h/mL)	AM (SD)	476 (464)	913 (569)	1670 (884)	4050 (1850)	1320 (1010)	2950 (1430)	925 (558)	*3330*[b]
C_{max} (ng/mL)	AM (SD)	98.3 (82.7)	158 (88.2)	240 (94.4)	505 (203)	205 (110)	400 (106)	155 (74.5)	*340*[b]
T_{max} (h)	Median	1.5	1.5	1.75	2.01	1.50	1.50	1.50	N/A
$t_{1/2}$ (h)	AM (SD)	ND	7.55 (3.16)	ND	6.70 (1.49)	ND	6.83 (1.96)	ND	N/A

Abbreviations: AM = arithmetic mean; SD = standard deviation; N = number of subjects, QD = once daily; Q12H = every 12 hours; N/A=not applicable
Note: Subjects were not dosed on Day 7 in the 50 mg Q12H cohort; therefore, PK parameters were predicted using population PK modeling.
[a] AUC_{tau} represents $AUC_{0\text{-}24}$ for 30, 60, and 70 mg QD BBP-671 treatments; AUC_{tau} represents $AUC_{0\text{-}12}$ for 50 mg Q12H BBP-671 treatment.
[B] 50 mg Q12H Day 7 PK parameters predicted using population PK modeling performed by Certara.

- BBP-671 was readily absorbed after oral administration with a T_{max} of ~1–2 hours and $t_{1/2}$ averaged 6–8 hours.
- The increase in exposure was more than dose-proportional as the total daily dose increased from 30 mg to 100 mg.
- The presence of food delayed absorption of BBP-671 by ~2 hours and showed a modest increase in plasma exposure (~1.3-fold), which was not considered clinically relevant.
- Urinary excretion of BBP-671 was negligible (<1% of the administered dose).



BBP-671 in CSF

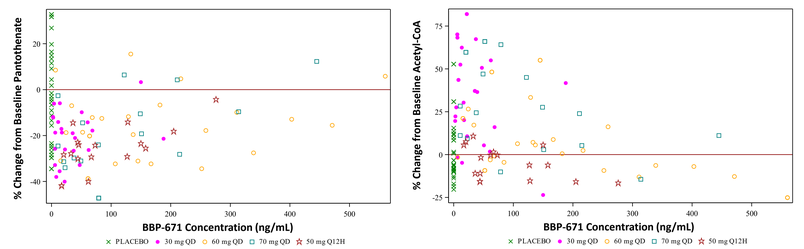
Day 6, 70 mg BBP-671 QD (N=4)		
Statistic	CSF Concentration	Partition Coefficient (CSF/Plasma)
GM (% GCV)	8.33 (20.6)	0.0241 (26.7)

Abbreviations: GM = geometric mean; % GCV = percent geometric coefficient of variation; N = number of subjects, QD = once daily
Note: CSF samples were collected ~2 hours post-dose. A plasma PK sample was also collected immediately after the lumbar puncture.

- BBP-671 was detected in the CSF in all subjects dosed 70 mg QD at steady state.
- Geometric mean ratio of the partition coefficient (CSF/plasma) was 0.0241, showing approximately 2.4% of systemic plasma concentrations penetrated the CSF.

PK-PD Relationship of BBP-671

PK-PD relationship of BBP-671 & plasma pantothenate | **PK-PD relationship of BBP-671 & whole blood acetyl-CoA**



- In MAD cohorts at steady-state, decreases in the PanK substrate, pantothenate, were observed, concurrent with increases in the PanK product, acetyl-CoA, in whole blood.
- Increases in whole blood acetyl-CoA were observed up to plasma BBP-671 concentrations of ~200 ng/mL.
- Decreases in plasma pantothenate were observed across BBP-671 exposures tested.
- Changes in pantothenate and acetyl-CoA demonstrated target engagement in a peripheral compartment in healthy adult subjects.

Conclusions & Clinical Implications

- BBP-671 was generally well-tolerated in 77 healthy adult subjects in a Phase 1 study.
  - No SAEs were observed.
  - The most common mild treatment-related TEAEs were headache, abdominal pain, and nausea.
  - Asymptomatic neutropenia was observed in 3 of 22 subjects with repeat BBP-671 dosing. All returned to within normal limits within a few days without any sequelae upon cessation of therapy.
- BBP-671 was orally bioavailable and was detected in CSF, indicating BBP-671 crossed the blood brain barrier.
- BBP-671 increased whole blood acetyl-CoA levels and decreased plasma pantothenate levels in healthy adult subjects, demonstrating target engagement and proof of mechanism.
- Based on these data, BBP-671 will be studied in patients with propionic acidemia and methylmalonic acidemia in the second half of 2022 and in PKAN patients in 2023.

References

1. L. K. Sharma, C. Subramanian, M. K. Yun, M. W. Frank, S. W. White, C. O. Rock, R. E. Lee, S. Jackowski, A therapeutic approach to pantothenate kinase associated neurodegeneration. Nat. Commun. 9, 4399 (2018).
2. Y. Li, J. Steinburg, Z. Coleman, S. Wang, C. Subramanian, Y. Li, Z. Patay, W. Akers, C. O. Rock, S. Jackowski, P. Bagga, Proton magnetic resonance spectroscopy detects cerebral metabolic derangement in a mouse model of brain coenzyme a deficiency. J. Transl. Med. 20, 103 (2022).