A Double-Blind Ascending Dose Placebo-Controlled Phase 2a Study of ABP-671, a Novel, Potent and Selective URAT1 Inhibitor, in Patients with Gout or Hyperuricemia

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ABSTRACT

ABP-671, a new selective and potent URAT1 inhibitor reduces reabsorption of uric acid (UA) from renal proximal tubules, and significantly decreases serum uric acid (sUA) levels in gout or hyperuricemia patients.

In this randomized, double-blind, ascending dose study, 60 participants (20/group and 10/cohort) were enrolled in successive ascending dose groups of 2 mg/placebo, 4 mg/ placebo, or 8 mg/placebo daily. Each dose group was subdivided into QD and BID cohorts (1:1) and randomized to receive ABP-671 oral tablets or matching placebo in an 8:2 ratio. To moderate rapid increases in urinary uric acid (uUA), subjects underwent a run-in period of 1 – 3 weeks. Safety labs were obtained at each visit, and serial blood and urine samples were collected for pharmacodynamic and pharmacokinetic studies in each dose cohort. Adverse events, safety laboratory tests, vital signs, and EKGs were collected throughout the study.

This study demonstrated a substantial and dose-dependent sUA lowering effect. Group mean and median sUA decreased rapidly in ABP-671 dosing groups during the first 7 days of run-in and further decreased in an apparently dose-proportional manner during the 28 days of dose evaluation. A clinical meaningful decrease in sUA levels was demonstrated after each run-in period and the respective dose evaluation period. By the end of the 28-day Dose Evaluation period, the median sUA level of the 2 mg group declined to 5.0 mg/dL and for the 4 mg and 8 mg groups, median sUA decreased to 3.8 mg/dL and 3.2 mg/dL respectively. Participant sUA levels reverted to pre-treatment levels 7 days after discontinuation of study drug. ABP-671 was well tolerated, without evidence of dose limiting toxicity. These results support the potential utility of ABP-671 when given once or twice-daily to treat hyperuricemia or gout.

In this study, ABP-671 was well tolerated at all doses tested. Gout flares occurred in 16 subjects – 3 in the 2 mg, 6 in the 4 mg, 5 in the 8 mg dose groups, and 2 in the pooled placebo groups. 3 participants developed transient renal stones – 2 participants receiving placebo and 1 participant receiving ABP-671. Study drug was discontinued only in 1 ABP-671 participant (4 mg BID) due to a gout flare, and in 1 placebo participant due to nephrolithiasis. There were no other AEs or lab abnormalities of potential concern.

BACKGROUND AND RATIONALE:

- Sustained hyperuricemia is the most significant risk factor for the development of gout
- Pharmacologic therapies for chronic gout focus on lowering sUA levels
- It can be difficult to reach the sUA treatment goals of < 6.0 and ≤ 5.0 mg/dL with current gout medications
  - ABP-671 is a novel URAT1 inhibitor that blocks reabsorption of UA within the renal proximal tubule and may significantly decrease sUA levels
- A Phase 1b placebo controlled-trial previously confirmed safety/sUA lowering of ABP-671 0.5 and 1.0 mg administered X10 days
- This Phase 2a study was designed to evaluate the safety, sUA lowering , pharmacokinetics (PK), and pharmacodynamics (PD) of multiple ascending oral doses of ABP-671 in adults with gout or hyperuricemia

ELIGIBILITY:

- ≥ 18 and ≤ 75 years
- BMI ≤ 40 kg/m^2
- Diagnosis of gout
- Serum uric acid (sUA ≥ 7.5 mg/dL and ≤ 12.5 mg/dL) at baseline
- No clinically significant kidney abnormalities noted on renal ultrasound

METHODS

- Using an ascending dose, double blind design, 60 participants were randomized successively to ABP-671 2 mg QD or 1 mg BID (Group 1); 4 mg QD or 2 mg BID (Group 2), 8 mg QD or 4 mg BID (Group#) or to matching placebo
- In order to avoid too rapid an increase in UA excretion and potentially resulting in tubular precipitation of uric acid, ABP-671 was gradually increased during a Run-in Period, followed by a 4-week Dose Evaluation Period
  - Group 1 (total daily dose 2 mg ABP-671):
    - Run-in: 1 mg ABP-671/Placebo QD X7 days
    - Dose Evaluation/Treatment Period: 1 mg ABP-671/ Placebo BID or 2 mg ABP-671/Placebo QD X28 days
  - Group 2 (total daily dose 4 mg ABP-671):
    - Run-in: 1 mg ABP-671/Placebo QD X7 days, followed by 2 mg ABP-671/Placebo QD X7 days
    - Dose Evaluation/Treatment Period:, 2 mg ABP-671/Placebo BID or 4 mg ABP-671/Placebo QD X28 days
  - Group 3 (total daily dose 8 mg ABP-671):
    - Run-in: 1 mg ABP-671/Placebo QD X7 days, followed by 2 mg ABP-671/Placebo QD X7 days followed by 4 mg ABP-671/Placebo X7 days
    - Dose Evaluation/Treatment Period: 4 mg ABP-671/Placebo BID or 8 mg ABP-671/Placebo QD X28 days
- Participants were to remain on gout flare prophylaxis medication until the end of at least the first Follow-up visit
- Safety, PK, and PD assessments were performed during the Dose Evaluation Period
- Safety labs, sUA, serum creatinine, adverse events, vital signs, EKGs were obtained at each visit

RESULTS

At the end of the 4-week dose evaluation period, mean sUA levels ranged from 3.1 to 5.3 for the 6 ABP-671 dose cohorts compared to 9.1 mg/dL for the combined placebo cohorts. All participants administered ABP-671 daily, irrespective of dose frequency (QD or BID), met the primary efficacy endpoint, mean percentage change in sUA levels from Baseline to the end of the 4-week Dose Evaluation Period significantly greater than placebo (Table 1). The difference between the active treatment and corresponding placebo cohorts was significant in all cases, with P < 0.0001. Mean reductions in sUA levels from Baseline at the end of the 4-week Dose Evaluation Period were -36%, -51%, -59% for the 2 mg, 4 mg, and 8 mg groups compared to increases of 7%, 1% and 13% in the placebo groups (all P < 0.0001).

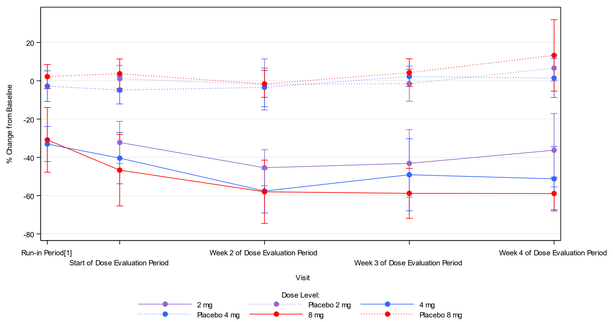

Figure 1. sUA for Modified ITT by Week
Abbreviations: mITT = Modified intent to treat.
Vertical Bar represents the standard deviation.
[1] 2 mg: 1 week run-in ; 4 mg: 2 weeks run-in ; 8 mg: 3 weeks run in.

Table 1. Percentage Change (SD) from Baseline in Serum Uric Acid by Cohort (mITT)

Treatment		Start of Dose Evaluation Period	Week 2 of Dose Evaluation Period	Week 3 of Dose Evaluation Period	Week 4 of Dose Evaluation Period
1 mg BID[a]	ABP-671 (N = 8)	-33.00 (9.98)	-49.78 (8.98)	-51.03 (11.02)	-39.20 (18.58)
	Placebo (N = 2)	6.72 (1.18)	8.57 (6.57)	4.90 (6.93)	7.81 (8.37)
2 mg QD[a]	ABP-671 (N = 8)	-31.46 (12.60)	-41.61 (8.45)	-37.26 (19.98)	-33.36 (20.62)
	Placebo (N = 2)	-4.51 (3.90)	-12.41 (7.26)	-7.96 (6.11)	5.46 (7.71)
2 mg BID[a]	ABP-671 (N = 8)	-41.13(14.86)	-64.16 (9.37)	-54.75 (22.43)	-63.12 (7.88)
	Placebo (N = 2)	-7.84 (7.95)	-11.47 (2.63)	-0.96 (1.36)	-7.180 (0.73)
4 mg QD[a]	ABP-671 (N = 8)	-39.71 (12.76)	-51.88 (10.27)	-44.18 (14.78)	-40.83 (15.82)
	Placebo (N = 2)	-1.82 (7.71)	4.55 (6.43)	5.46 (0.00)	10.00 (3.86)
4 mg BID[a]	ABP-671 (N = 8)	-42.04 (25.40)	-58.64 (22.28)	-64.93 (9.80)	-61.66 (8.14)
	Placebo (N = 2)	9.36 (6.50)	3.49 (4.93)	9.47 (6.81)	28.32 (10.45)
8 mg QD[a]	ABP-671 (N = 8)	-51.34 (7.23)	-57.36 (9.34)	-53.50 (13.72)	-56.51 (8.54)
	Placebo (N = 2)	-1.96 (2.77)	-6.75 (4.31)	-0.98 (1.39)	-1.80 (5.32)

Abbreviations: BID = Twice daily; mITT = Modified intent-to-treat; N = Number of participants; QD = Once daily.

Table 2. Serum Uric Acid Categories at Week 4 by Cohort (mITT Population)

Serum uric acid (sUA) Level at Week 4	ABP-671 1 mg BID (N=8)	ABP-671 2 mg QD (N=8)	ABP-671 2 mg BID (N=7)	ABP-671 4 mg QD (N=8)	ABP-671 4 mg BID (N=7)	ABP-671 8 mg QD (N=8)	Placebo (N=12)
sUA < 6 mg/dL	6 (75.0%)	5 (62.5%)	7 (100.0%)	7 (87.5%)	7 (100.0%)	8 (100.0%)	0
sUA < 5 mg/dL	3 (37.5%)	3 (37.5%)	7 (100.0%)	5 (62.5%)	7 (100.0%)	8 (100.0%)	0
sUA < 4 mg/dL	1 (12.5%)	0	6 (85.7%)	1 (12.5%)	6 (85.7%)	7 (87.5%)	0

Abbreviations: BID = Twice daily; CI = Confidence interval; mITT = Modified intent-to-treat; N = Number of participants; QD = Once daily.

- Following 7 days of 1 mg ABP-671 QD administration in 48 participants (ie, the Run-in Period), more than half (26 [54%] of 48 participants) had a ≥30% reduction in sUA levels, with 27 (56%) reaching a target sUA of < 6 mg/dL
- The mean percentage reductions in the sUA levels from Baseline at the end of the 4-week Dose Evaluation Period increased with increasing daily dose of ABP-671; however, there was a large variability among individuals on the same total daily dose. There was a consistently greater reduction in mean sUA with BID dosing compared to QD dosing; however, it only reached statistical significance in the 4 mg daily dose group (P = 0.0005)
- Overall, 11 (70%) of 16 participants treated with a total daily dose of 2 mg ABP-671 achieved sUA levels of < 6 mg/dL at the end of the 4-week Dose Evaluation Period, 14 (89%) of 16 participants treated with a total daily dose of 4 mg ABP-671, and 15 (948%) of 16 participants treated with a total daily dose of 8 mg ABP-671
- No participants treated with placebo achieved sUA levels of < 6 mg/dL at the EOT. There was a clear dose relationship between efficacy and ABP-671 dose
- At the end of 4 weeks of dosing, more participants in the 2 mg BID cohort reached target sUA levels of < 5 mg/dL and < 4 mg/dL (100% and 85.7%, respectively) than in the 4 mg QD cohort (63% and 13%, respectively). No such difference between BID and QD dosing regimens was observed in the 2 mg and 8 mg total daily dose groups

SAFETY

- Overall, 48 (80%) of 60 participants had TEAEs during the study
  - TEAE incidence was similar between pooled placebo and the pooled ABP-671 groups
    - 10 of 12 [83%]) placebo and 38 of 48 [79%] ABP-671 recipients
    - TEAE incidence was similar across all ABP-671 daily dose levels (2 mg, 4 mg, or 8 mg), irrespective of dose frequency (BID / QD), ranging from 75% to 88% of the 6 ABP-671 treatment cohorts
- Most TEAEs were mild (29 [48%] of 60 participants) or moderate (17 [28%] of 60 participants) in severity. There were no severe (Grade 3) TEAEs in the ABP-671 treatment groups. There were 3 severe TEAEs in 2 participants who received placebo (including 1 event of nephrolithiasis and 1 event of renal colic in 1 participant; and 1 event of dyspnea in another participant). Only 2 (3%) of 60 participants had SAEs (1 participant had shortness of breath and 1 participant had renal colic), both of whom were in the placebo group. There were no life-threatening or fatal events
- Study drug was withdrawn due to TEAEs in 2 participants
  - One participant in the 1 mg placebo BID cohort (a 48-year-old male) with severe renal colic/nephrolithiasis assessed as probably related to study drug (i.e., placebo)
  - One participant in the 4 mg ABP-671 BID cohort (a 41-year-old male) experienced a moderate gout flare assessed as unrelated to the IP. ABP-671 was discontinued and the event resolved within 5 days
- Treatment-emergent adverse events of special interest (TEAESIs), (clinically significant events of acute gout attacks or nephrolithiasis), occurred in 19 participants overall:
  - Sixteen (27%) participants had gout attacks (flares) on study
    - 3 (19%) of 16 participants in the 2 mg ABP-671 total daily dose group
    - 6 (38%) of 16 participants in the 4 mg ABP-671 total daily dose group
    - 5 (31%) of 16 participants in the 8 mg ABP-671 total daily dose group
    - 2 (17%) of 12 participants in the pooled placebo group
  - Three (5%) of 60 participants had nephrolithiasis:
    - 1 (2%) of 48 participants in the 4 mg ABP-671 BID cohort
    - 2 (17%) of 12 participants in the placebo group
    - All 3 events of nephrolithiasis were assessed by the PI as unrelated to study drug

DISCUSSION AND CONCLUSIONS:

- All participants administered 2 mg, 4 mg, or 8 mg of ABP-671 daily, irrespective of dose frequency (BID or QD), met the primary efficacy endpoint of a significant reduction in sUA levels compared to those administered placebo by the end of the 4-week Dose Evaluation Period (all P <0.0001)
- At the end of the 4-week Dose Evaluation Period, ABP-671 recipients, and no placebo recipients had substantial dose-related decreases in sUA with sUA levels below as low as 5mg/dL or 4 mg/dL(as shown in Table 2). Reducing sUA to less than 4 or 5 mg/dL may initiate dissolution of urate crystal deposits and reduce tophus size
- More participants in the 2 mg BID cohort reached target sUA levels of < 5 mg/dL and < 4 mg/dL (100% and 86%, respectively) than in the 4 mg QD cohort (63% and 13%, respectively). No such difference between BID and QD dosing regimens was observed in the 2 mg and 8 mg total daily dose groups
- Following multiple oral administration of 1 mg BID, 2 mg BID, and 4 mg BID ABP-671
  - The median T_{max} ranged from 2.00 to 3.00 hours, and the rate and extent of systemic exposure (as measured by C_{max} and AUC) increased 4-fold for a 4-fold increase in dose (ie, 1 mg BID to 4 mg BID)
  - The terminal half-life ($t_{½}$) of ABP-671 was low, with a mean range of 3.22 to 3.82 hours across all BID dose cohorts
  - Clearance and terminal volume of distribution of ABP-671 were in the range of 3.83 to 4.46 L/hour and 17.01 to 20.59 L/hour, respectively, and comparable across all BID dose cohorts
- Following multiple oral administration of 2 mg QD, 4 mg QD, and 8 mg QD ABP-671
  - The median T_{max} ranged from 1.98 to 2.02 hours, and the rate and extent of systemic exposure (as measured by C_{max} and AUC) increased 5-fold for a 4-fold increase in dose (ie, from 2 mg QD to 8 mg QD)
  - The terminal half-life ($t_{½}$) of ABP-671 was low, with a mean range of 3.22 to 4.01 hours across all QD dose cohorts
  - Clearance and terminal volume of distribution of ABP-671 were in the range of 4.14 to 5.10 L/hour and 17.52 to 20.72 L/hour, respectively, and comparable across all QD dose cohorts
- ABP-671 was also well tolerated, with the overall incidence of TEAEs similar between the ABP-671 treatment cohorts and the placebo group. Most TEAEs were mild (29 [48%] of 60 participants) or moderate (17 [28%] of 60 participants) in severity. There were no severe TEAEs, life-threatening or fatal events

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