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ORIGINAL RESEARCH

Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Food Effects of Single and Multiple Oral Doses of ABP-671 in Healthy and Hyperuricemic Subjects

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Purpose: To evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and food effects of single and multiple oral doses of ABP-671, a novel URAT1 inhibitor, in healthy and hyperuricemic subjects.

Patients and Methods: This placebo-controlled study of ABP-671 was conducted in the United States, and contained three parts: a. single ascending dose (SAD); b. multiple ascending dose (MAD); c. food effect. The study doses of SAD part, 0.1, 0.5, and 1.0 mg, and placebo oral solutions were investigated in healthy volunteers. In the MAD study, hyperuricemic but otherwise healthy subjects received 0.2, 0.5, or 1.0 mg/d of ABP-671 or placebo oral solutions for 10 days. In the food effect study, healthy subjects received 1.0 mg ABP-671 tablet in the fasted or fed state in a crossover design.

Results: A total of 24, 27, and 12 subjects were enrolled, with 5, 9, and 5 treatment-emergent adverse events (TEAEs) observed in the SAD, MAD, and food effect studies, respectively. There were no serious adverse events (SAEs) or TEAEs leading to discontinuation or death. In the SAD and MAD studies, the peak plasma concentration and areas under the curves increased with the increasing drug doses. The serum uric acid (sUA) levels started decreasing 3 hours after ABP-671 administration, and the percentage changes from baseline for sUA increased with the increasing drug doses. Fasting or postprandial state did not affect the PK of ABP-671.

Conclusion: Single or multiple oral doses of ABP-671 are well tolerated at doses 0.1, 0.5 and 1.0 mg for the SAD, 0.2, 0.5, and 1.0 mg/d for the MAD, and 1.0 mg for the food effect study. A proportional relationship between dose and exposure was observed. ABP-671 reduced the sUA levels with a rapid (3 hours) onset and in a dose responsive manner.

Keywords: ABP-671, safety, pharmacokinetics, pharmacodynamics, food effect, hyperuricemia, serum uric acid

Introduction

Gout is a chronic disease characterized by high serum uric acid (sUA) levels caused by purine metabolism and/or uric acid excretion disorders.[1–3] The reported prevalence of gout ranges from <1% to 6.8% with an incidence of 0.58–2.89 per 1000 person-years depending on populations studied and methods used.[4] When sUA is improperly managed, chronic joint inflammation may develop, as well as tophi, which are mass-like deposits of crystals surrounded by inflammatory aggregates and fibrous capsules. Tophi can damage bone and cartilage permanently. In addition to diet and lifestyle interventions, urate-lowering therapy (ULT) is often utilized in gout management with the long-term goal of controlling the sUA levels to <6 or <5 mg/dL.[5–7]

ULTs include xanthine oxidase inhibitors (eg, febuxostat and allopurinol), URAT1 inhibitors (eg, benzbromarone, probenecid and lesinurad [withdrawn worldwide in 2019]), and urate oxidase (eg, pegloticase).[5,7] These drugs have several limitations, such as unsatisfactory therapeutic effects and severe liver and kidney toxicities.[5,7] Febuxostat can even lead to an increased risk of cardiovascular events.[8] Therefore, there is an urgent need to develop new, safe, and more effective ULT drugs.

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URAT1 is primarily expressed in the epithelial cells of proximal tubules in the renal cortex and plays an important role in uric acid (UA) reabsorption (about 90%).[9] ABP-671 is a novel URAT1 inhibitor, developed by Atom Therapeutics Co., Ltd, that lowers the sUA levels by reducing the reabsorption of UA in the kidney and promoting the excretion of UA through urine. In vitro experiments using Madin Darby canine kidney cells with stable expression of human URAT1 showed that ABP-671 inhibited URAT1-mediated uric acid transport with an IC_{50} of 0.04 μM, significantly lower than those of benzbromarone (0.14 μM) and lesinurad (24.36 μM). In vivo experiments in hyperuricemic rats showed that ABP-671 was rapidly absorbed after administration, and the levels of sUA and blood urea nitrogen could be significantly reduced at doses of 15 and 25 mg/kg/d (unpublished data).

This study aims to examine the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and food effects of single and multiple oral doses of ABP-671 in healthy volunteers and subjects with hyperuricemia.

Patients and Methods

Study Design

This study of ABP-671 was conducted in healthy subjects and hyperuricemic subjects in the United States, and contained the following three parts:

Single Ascending Dose (SAD) Study

This single-center, randomized, double-blind, placebo-controlled Phase I study evaluated the safety, tolerability, PK, and PD of single ascending doses of ABP-671 in healthy subjects. In the SAD study, the doses of ABP-671 given were designed as 0.1, 0.5, and 1.0 mg, with two placebo controls and six subjects per dose group. After an 8-hour overnight fast, the subjects were administered a single oral dose of ABP-671 or placebo with 240 mL of water.

Each dose cohort consisted of eight subjects who received a single oral dose of ABP-671 (n=6) or placebo (n=2) in a double-blind manner and a fasted state. In each cohort, two sentinel subjects were randomly assigned so that one received ABP-671 and one received a placebo. If the dosing of these two subjects proceeded without any safety issues in the 72 hours following administration, the remaining six subjects in each cohort were dosed with either ABP-671 (n=5) or placebo (n=1) according to the randomization schedule. Once all eight subjects from one cohort completed the treatment, followed by at least 7 days of observation, the next higher dosage was administered to the two sentinel subjects in the next cohort (Figure 1A).

Multiple Ascending Dose (MAD) Study

This randomized, double-blind, placebo-controlled Phase 1b study evaluated the safety, tolerability, PK, and PD of ascending oral doses of ABP-671 solution administered once daily (QD) for 10 days in subjects with hyperuricemia (sUA ≥7.0 mg/dL for males and ≥6.0 mg/dL for females) who were otherwise healthy. ABP-671 was administered orally as a 10 mL aqueous solution of 3% sodium bicarbonate with 480 mL of water following an overnight fast on days 1–10.

This study included three ascending oral dose cohorts at dose levels of 0.2, 0.5, and 1.0 mg/d. Nine subjects were enrolled in each cohort and dosed with ABP-671 (n=7) or placebo (n=2) in a fasted state, QD, for 10 consecutive days according to the randomization scheme. Once all nine subjects from one cohort had completed 10 days of dosing and 14 days of safety follow-up, the next cohort was enrolled (Figure 1B). The subjects who dropped out for reasons other than treatment-related adverse events (AEs) were replaced.

Food Effect Study

In this single-center, open-label, single-dose, two-way randomized, crossover study, 12 healthy subjects were randomized to one of two treatment sequences (AB or BA) in Pharmaron Clinical Pharmacology Center, USA (Figure 1C). Treatments A and B were a single oral dose of ABP-671 1.0 mg tablet in fasted and fed states, respectively, administered with approximately 240 mL of water. Each treatment period was separated by a washout interval of 4 days.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice of the International Council for Harmonisation. All pertinent study documents were reviewed and approved by the Advarra

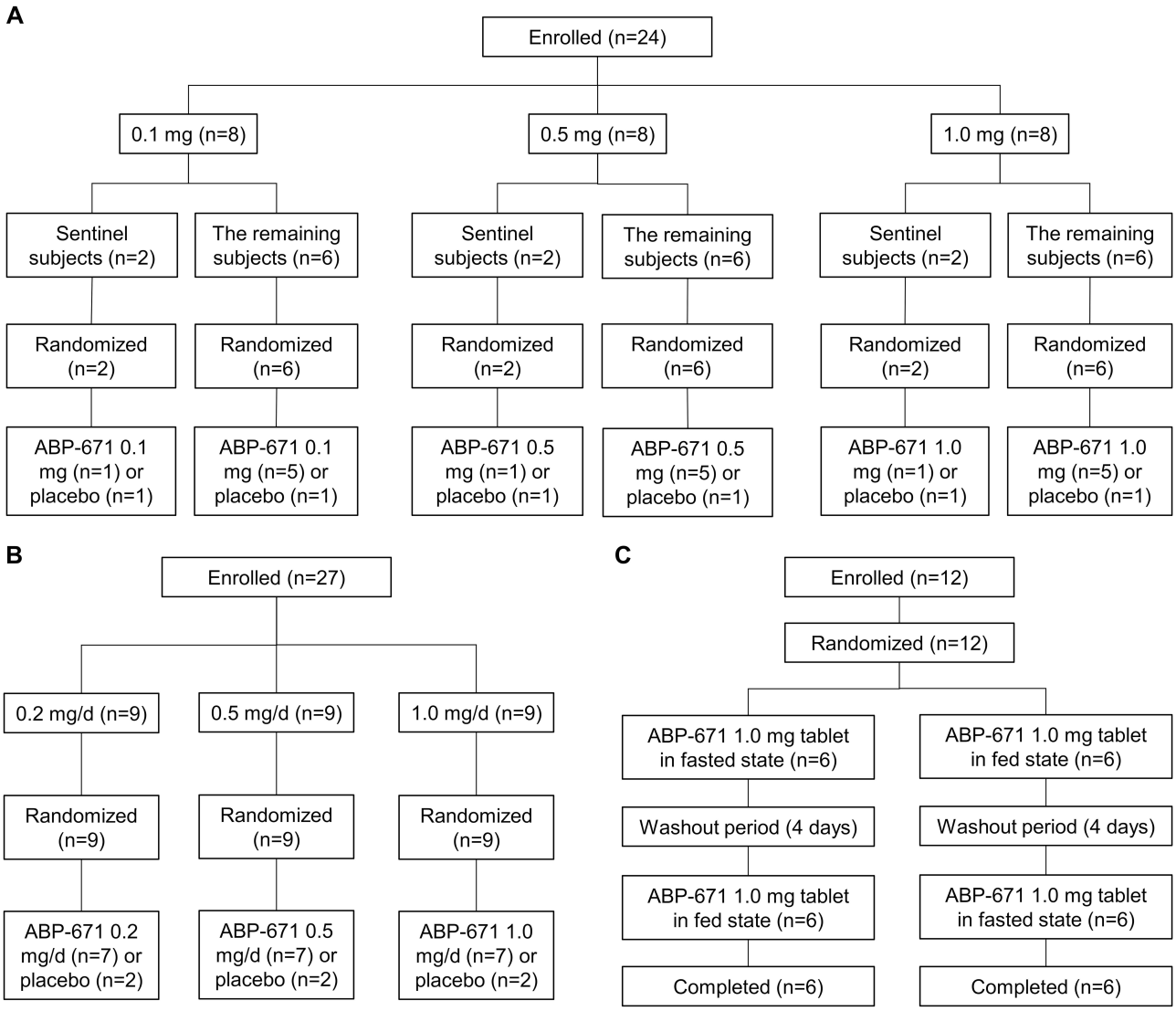

Figure 1 Clinical trial design. (**A**) Single ascending dose study. (**B**) Multiple ascending dose study. (**C**) Food-effect study.

Institutional Review Board (Approval No.: MOD00398822 & MOD00507949), the IntegReview Institutional Review Board (Approval No.: IRB00008463, IRB00003657, IRB00004920, IRB00001035, IRB00006075) prior to study initiation. The subjects provided written informed consent prior to initiation of any study-specific procedures. The trials were registered with clinicaltrials.gov (SAD: NCT03906006; MAD: NCT04060173; food effect study: NCT04303039).

Study Population

SAD Study

Key inclusion criteria: (1) aged 18 to 45 years; (2) healthy subjects determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and vital signs at screening; (3) sUA ranged 4.0 to 5.5 mg/dL for males and 4.0 to 5.0 mg/dL for females at screening; (4) body mass index (BMI) of 18.0 to 32.0 kg/m^2; (5) body weight of ≥50 kg.

Key exclusion criteria: (1) history or clinical manifestations of significant systemic diseases or psychiatric disorders; (2) history or suspicion of kidney stones; (3) previous use of prescription drugs, over-the-counter drugs, or herbal remedies within 14 days before Day 1 of study medication dosing, or females who had received hormone replacement therapy (HRT) within 28 days prior to dosing; (4) positive for urine drug screening tests; (5) major surgery within 3 months prior to Day 1; (6) any other conditions inappropriate for participation in the judgment of the investigator.

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MAD Study

Key inclusion criteria: (1) hyperuricemic but otherwise medically documented as healthy; (2) aged 18 to 65 years; (3) sUA ranged ≥7.0 mg/dL for males and ≥6.0 mg/dL for females based on an average value of the first screening visit and Day −1; (4) BMI of 18.0 to 35.0 kg/m^2; (5) body weight of ≥50 kg.

Key exclusion criteria: (1) history or clinical manifestations of significant systemic diseases or psychiatric disorders; (2) ≥1 episode(s) of arthritis, not including gout arthritis, within the last 6 months; (3) a flare of gout in the past 6 months; (4) history or suspicion of kidney stones; (5) previous use of prescription drugs, over-the-counter drugs, or herbal remedies within 3 weeks before Day 1 of study medication dosing; (6) positive for urine drug screening tests; (7) major surgery within 3 months prior to Day 1; (8) received any investigational test drug, including ABP-671, within 5 half-lives or 30 days, whichever was longer, prior to Day 1 study medication dosing; (9) prior exposure to ABP-671; (10) any other conditions inappropriate for participation in the judgment of the investigator.

Food Effect Study

Key inclusion criteria: (1) aged 18 to 60 years; (2) healthy subjects determined by medical history, physical examination, 12-lead ECG, and vital signs at screening; (3) sUA ≥3.7 and <7.0 mg/dL for males, and ≥2.3 and <6.0 mg/dL for females at screening; (4) BMI of 18.0 to 35.0 kg/m^2; (5) body weight of ≥ 50 kg.

Key exclusion criteria: (1) history or clinical manifestations of significant systemic diseases or psychiatric disorders; (2) history of bariatric surgery, intestinal resection, malabsorption, or celiac diseases except appendectomy; (3) history or suspicion of kidney stones; (4) history of gout; (5) previous use of prescription drugs, over-the-counter drugs, or herbal remedies, or females who had received HRT within 14 days before dosing on Day 1; (6) positive for urine drug and alcohol screening tests; (7) major surgery within 3 months prior to Day 1; (8) received any investigational product within 5 half-lives or 30 days; (9) previously received ABP-671; (10) any other conditions inappropriate for participation in the judgment of the investigator.

PK and PD Assessments

Blood samples for the PK (approximately 5 mL) and PD analyses (approximately 2 mL) and urine samples for PD analysis were collected at the time points indicated in Supplementary Table S1. The drug concentration in plasma and urine was determined by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The PK and PD parameters were calculated with non-compartmental methods using Phoenix® WinNonlin® Version 8.1 (Pharsight Corporation, Mountain View, CA).

Analysis of Food Effects

To analyze the food effects, an analysis of variance and a linear model were used to analyze the log-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} with dietary state (fed vs fasted). The standard model sequence, period, and treatment were used as a fixed effect, and subjects nested within the sequence as a random effect. The geometric mean ratios (GMRs) and associated 90% CIs were calculated. If the 90% CI of GMR fell into 80.00%-125.00%, food was considered to have no significant effect on the exposure of ABP-671.

Safety Monitoring

The safety assessments included AEs and serious AEs (SAEs), ECGs, vital signs, physical examinations, and safety laboratory tests. In the SAD study, all subjects underwent safety assessments at screening, pre-dose (day −1 to day 1), days 1–4, and follow-up visits (day 7, day 14, and day 28). In the MAD study, all subjects underwent safety assessments at screening, pre-dose (day −1 to day 1), days 1–13, and follow-up visits (day 17, day 24, and day 38). In the food effect study, all subjects underwent safety assessments at screening, pre-dose of period 1 (day −1 to day 1), days 1–4, pre-dose of period 2 (day 5 to day 6), days 6–9, and follow-up visit (day 12), and day 19. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 22.0. The severity of all AEs was graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.

Statistical Analysis

The safety and PD analysis sets included the subjects who received ABP-671 or matching placebo at least once. The PK analysis set included the subjects who received ABP-671. Data from subjects who received the placebo treatment were pooled across cohorts. Demographic characteristics were summarized using mean ± standard deviation (SD) or number (percentage). PK and PD parameters were summarized using geometric mean (geometric CV%) or median (range). The safety assessments after administration were summarized descriptively.

Results

Subjects Enrollment and Characteristics

A total of 24 healthy subjects were enrolled in the SAD study, including six subjects each for ABP-671 dosing groups (0.1, 0.5, and 1.0 mg) and six subjects for the placebo group. A total of 27 subjects with hyperuricemia were enrolled in the MAD study, including seven subjects each for ABP-671 dosing groups (0.2, 0.5, and 1.0 mg) and six subjects for the placebo groups. A total of 12 healthy subjects were enrolled in the food effect study, including six subjects each for the fasted-fed and fed-fasted groups. The mean age of all groups ranged from 30.7 to 47.1 years, and the mean BMI ranged from 22.93 to 30.97 kg/m^2 (Table 1). Male was the predominant gender in most cohorts, ranging from 50% to 100% (Table 1).

Safety and Tolerability

A summary of TEAEs is presented in Supplementary Table S2. The overall incidence of TEAEs was comparable between the ABP-671 and placebo groups. In the SAD study, one (17%), one (17%), two (33%), and one (13%) subject reported TEAEs in the 0.1 mg, 0.5 mg, 1.0 mg, and placebo groups, respectively. All TEAEs were graded as mild or moderate. (Supplementary Table S2).

In the MAD study, two (29%), four (57%), one (14%), and two (33%) subjects in the 0.2 mg/d, 0.5 mg/d, 1.0 mg/d, and placebo groups, respectively, reported TEAEs, most of which were grade 1. (Supplementary Table S2).

In the food effect study, there were three (25.0%) and two (16.7%) TEAEs in the fasted and fed states, respectively. All TEAEs were grade 1 (Supplementary Table S2).

There were no TEAEs leading to discontinuation or death in any of the three studies.

PK

The plasma concentration-time curves for the dose groups of ABP-671 in the SAD study are presented in Figure 2A and B. In the 0.1, 0.5, and 1.0 mg dose groups, the range of median t_{max} was 0.695–1.006 h; the range of mean CL/F was 3.436–3.651 L/h; and the range of mean $t_{1/2}$ was 3.095–4.575 h. C_{max}, AUCs and V_d/F increased with increasing doses (Table 2).

In the MAD study, the plasma concentration-time curves for each dose group of ABP-671 on days 1, 5, and 10 are shown in Figure 2C and D. On day 10, the range of median $t_{max,ss}$ was 1.000–1.003 h; the range of mean CL_{ss}/F was 5.042–5.992 L/h; and the range of mean $t_{1/2}$ was 2.622–2.964 h. $C_{max,ss.}$ AUC_{tau} increased with the increasing dose (Table 2).

Dose proportionality was observed for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} in both SAD and MAD studies as all CIs for slope have a value of 1 (Table 3).

PD

In the SAD study, the sUA levels started decreasing 3 hours after ABP-671 administration, and the percentage reduction from baseline in sUA increased with the increasing drug dose. The maximum percentage changes from baseline in sUA were observed at 12–24 hours after administration, reaching 8.5%, 29.9%, and 34.6% in the 0.1, 0.5, and 1.0 mg groups, respectively. At 24 hours post-dose, the mean percentage changes from baseline in sUA were –6.8%, –23.8%, and –26.5% in the 0.1, 0.5, and 1.0 mg groups, compared with 2.1% in the placebo group (Supplementary Table S3). At

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Table 1 Characteristics of the Subjects

Study	SAD (n=24)				MAD (n=27)				Food effect (n=12)	
Group	0.1 mg (n=6)	0.5 mg (n=6)	1.0 mg (n=6)	Placebo (n=6)	0.2 mg (n=7)	0.5 mg (n=7)	1.0 mg (n=7)	Placebo (n=6)	Fasted-fed (n=6)	Fed-fasted (n=6)
Age (years), Mean ± SD	31.2±5.04	30.7±9.52	32.5±7.40	30.2±9.04	41.7±10.63	39.6±10.10	47.1±10.32	31.3±8.29	48.3±5.75	36.5±12.29
Sex (male)	4 (67%)	5 (83%)	4 (67%)	6 (100%)	7 (100%)	5 (71%)	7 (100%)	6 (100%)	3 (50.0%)	3 (50.0%)
Ethnicity (Hispanic or Latino)	5 (83%)	4 (67%)	4 (67%)	2 (33.3%)	5 (71%)	6 (86%)	3 (43%)	5 (83%)	2 (33.3%)	0
Weight (kg), Mean ± SD	69.58±4.43	67.25±6.59	75.92±9.23	75.82±9.39	91.81±8.67	89.76±9.94	93.73±10.72	95.78±12.10	80.48±12.93	79.62±10.03
Height (cm), Mean ± SD	174.5±7.34	169.0±6.75	170.7±7.81	173.8±9.64	174.1±9.67	172.1±7.78	177.9±6.74	175.5±8.41	175.12±13.75	171.30±11.75
BMI (kg/m^2), Mean ± SD	22.93±2.57	23.67±3.26	26.12±3.04	25.25±3.83	30.22±0.94	30.25±2.32	29.46±2.82	30.97±2.31	26.37±4.20	27.12±2.07

Abbreviations: SAD: single ascending dose; MAD: multiple ascending dose; BMI: body mass index.

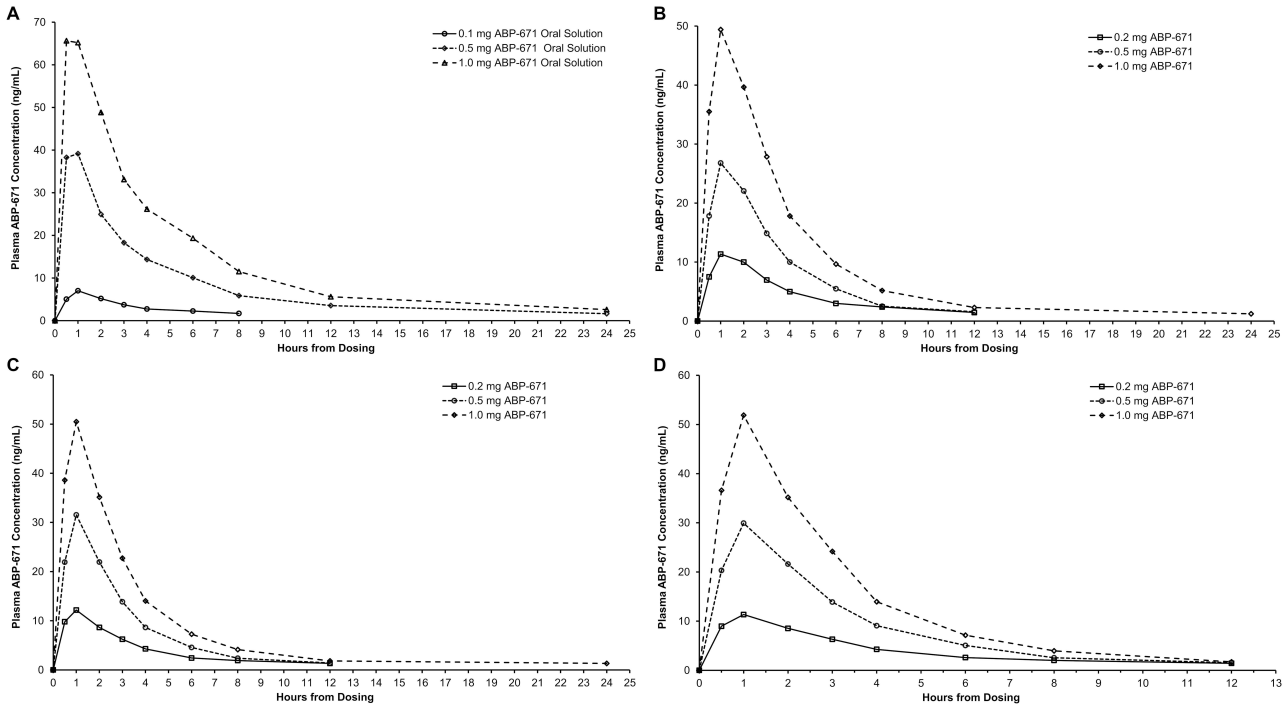

Figure 2 Plasma concentration-time curves of ABP-671. (**A**). The 0.1, 0.5, and 1.0 mg cohorts in the SAD study. (**B**) The 0.2, 0.5, and 1.0 mg cohorts on day 1 in the multiple ascending dose (MAD) study. (**C**) The 0.2, 0.5, and 1.0 mg cohorts on day 5 in the MAD study. (**D**) The 0.2, 0.5, and 1.0 mg cohorts on day 10 in the MAD study.

72 hours after administration, the sUA levels in the 0.1, 0.5, and 1.0 mg groups rebound back to close to the baseline level (Table 4, Supplementary Table S3 and Figure 3A).

In the MAD study, the sUA levels started decreasing 3 hours after administration in all dose groups on day 1. The percentage reduction from baseline in the sUA levels increased with the increasing drug dose. The maximum percentage sUA reduction from the baseline were −12%, −25%, and −28% for the 0.2, 0.5, and 1.0 mg dose groups, respectively. At

Table 2 PK Parameter Measurements in the SAD Study and on Day 10 in the MAD Study

SAD	**0.1 mg (n=6)**	**0.5 mg (n=6)**	**1.0 mg (n=6)**
AUC_{0-24} (ng*h/mL)	29.3 (43.6)	149.7 (52.8)	302.8 (40.0)
AUC_{0-t} (ng*h/mL)	23.0 (41.2)	144.2 (55.9)	294.7 (43.1)
AUC_{0-inf} (ng*h/mL)	29.6 (44.4)	152.7 (55.2)	311.8 (42.9)
$\%AUC_{extrap}$ (%)	22.1±4.77	5.6±1.02	5.5±1.81
C_{max} (ng/mL)	7.2 (13.4)	40.8 (21.6)	69.6 (16.9)
C_{last} (ng/mL)	1.6±0.41	1.8±0.44	2.8±0.81
t_{max} (h)	1.01 (0.50, 1.01)	0.75 (0.50, 1.01)	0.70 (0.50, 1.02)
t_{last} (h)	7.0 (4.0, 8.0)	12.0 (8.0, 24.0)	18.0 (12.0, 24.1)
Kel (1/h)	0.25±0.100	0.22±0.1053	0.17±0.071
$t_{1/2}$ (h)	3.1±1.12	3.8±2.00	4.6±1.80
CL/F (L/h)	3.65±1.623	3.59±1.385	3.44±1.373
V_d/F (L)	14.4±1.80	17.0±6.08	20.4±5.10
MAD Day 10	**0.2 mg (n=7)**	**0.5 mg (n=7)**	**1.0 mg (n=6)**
AUC_{tau} (ng*h/mL)	42.9 (48.7)	101.4 (23.7)	168.9 (17.3)
$C_{max,ss}$ (ng/mL)	11.1 (42.6)	29.6 (16.5)	51.4 (16.3)

(*Continued*)

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Table 2 (Continued).

SAD	0.1 mg (n=6)	0.5 mg (n=6)	1.0 mg (n=6)
$t_{max,ss}$ (h)	1.00 (0.50, 1.03)	1.00 (1.00, 1.05)	1.00 (0.51, 1.00)
Kel (1/h)	0.268±0.1041	0.278±0.0660	0.241±0.0297
$t_{1/2}$ (h)	2.96±1.231	2.62±0.644	2.92±0.423
RA, AUC	0.91±0.145	1.00±0.117	0.85±0.152
RA,C_{max}	0.99±0.114	1.10±0.211	1.01±0.224
CL_{ss}/F (L/h)	5.08±2.195	5.04±1.125	5.99±0.998

Notes: AUCs and C_{max} are presented as geometric mean (geometric CV%). t_{max} and t_{last} values are presented as median (min, max).

Abbreviations: SAD, single ascending dose; MAD, multiple ascending doses; AUC, area under the plasma concentration-time; C_{max}, peak plasma concentration; C_{last}, last observed plasma concentration; $\%AUC_{extrap}$, area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of the total AUC; t_{max}, time to reach the peak plasma concentration following drug administration; t_{last}, time to the last observation; Kel, fraction of drug eliminated per unit of time; $t_{1/2}$, half-life; CL/F, apparent total body clearance of drug from plasma after oral administration; V_d/F, apparent volume of distribution after non-intravenous administration; RA,AUC, accumulation ratio calculated from the $AUC_{\tau,ss}$ and AUC_{τ} after single dosing; RA,C_{max}, Accumulation ratio calculated from the $C_{max,ss}$ and C_{max} after single dosing.

Table 3 Dose Proportionality of PK Parameters

Study Day	PK Parameter	Estimate of Slope (b)	Standard Error	95% CI for Slope
SAD	AUC_{0-t} (ng*h/mL)	1.11	0.11	0.89–1.34
	AUC_{0-inf} (ng*h/mL)	1.02	0.11	0.80–1.25
	C_{max} (ng/mL)	1.00	0.05	0.91–1.10
MAD day 10	AUC_{tau} (ng*h/mL)	0.86	0.11	0.63–1.08
	$C_{max,ss}$ (ng/mL)	0.96	0.09	0.77–1.16

Abbreviations: SAD, single ascending dose; MAD, multiple ascending dose; AUC, area under the plasma concentration-time; C_{max}, peak plasma concentration.

24 hours post-dose, mean percentage reductions in sUA for the 0.2 mg, 0.5 mg, and 1.0 mg groups were –5.5%, –19.7%, and –20.6% on Day 1; –13.4%, –24.1%, and –30.4% on Day 5; and –11.7%, –22.2%, and –26.6% on Day 10, respectively. In contrast, the corresponding values in the placebo group were –1.1%, –4.4%, and –2.0% on those same days (Supplementary Table S4). On day 10, the maximum percentage reduction in sUA from the baseline were −23%, −39%, and −44% for the same dose groups, respectively. At 48 hours after drug administration on day 10, the sUA levels in the 0.5 and 1.0 mg groups decreased by about 14% compared to baseline, and 72 hours the sUA levels returned to close to the baseline level (Table 4, Supplementary Table S4, and Figure 3B–D). The percentage changes from baseline in UA fractional excretion for the SAD and MAD studies are presented in Table 4, Supplementary Tables S4 and Figure 4.

Food Effect

The values of AUC_{0-t}, AUC_{0-inf}, and C_{max} in the postprandial and fasting states were similar, and the 90% CIs of GMR were all within the range of 80%-125%. The values of sUA, percentage changes from baseline in sUA, UA excretion rate, E_{max}, and tE_{max} in the postprandial and fasting states were also similar between the fasting states, suggesting that food had no significant effect on the PK and PD parameters of ABP-671 (Table 5 and Figure 5).

Discussion

This three-part (SAD, MAD, and food effect) study aimed to evaluate the safety, tolerability, PK, PD, and food effect of single and multiple oral doses of ABP-671 in healthy and hyperuricemia subjects. The results indicate that single and

Table 4 PD Measurements in the SAD and MAD Studies

PD Parameters	SAD				MAD Day 1				MAD Day 5				MAD Day 10			
	0.1 mg (n=6)	0.5 mg (n=6)	1.0 mg (n=6)	Placebo (n=6)	0.2 mg (n=7)	0.5 mg (n=7)	1.0 mg (n=7)	Placebo (n=6)	0.2 mg (n=7)	0.5 mg (n=7)	1.0 mg (n=6)	Placebo (n=6)	0.2 mg (n=7)	0.5 mg (n=7)	1.0 mg (n=6)	Placebo (n=6)
E_{max} (mg/dL)	4.42±0.479	3.37±0.446	2.92±0.306	4.25±0.33	6.54±0.299	5.69±1.123	5.54±1.222	6.83±0.455	5.51±0.604	4.69±0.972	4.15±0.586	6.37±0.628	5.66±0.597	4.66±0.796	4.18±0.564	6.62±0.655
t_{Emax} (h)	3.03 (3.01, 48.0)	9.01 (3.01, 72.06)	12.01 (3.00, 12.05)	72.000 (3.00, 312.00)	12.01 (3.01, 12.06)	12.11 (6.00, 12.15)	6.01 (6.00, 12.02)	12.03 (3.02, 12.13)	6.02 (6.00, 12.05)	6.01 (3.00, 6.02)	6.03 (6.00, 6.03)	6.02 (6.01, 12.03)	6.02 (6.00, 12.00)	6.04 (2.98, 6.06)	6.01 (3.00, 6.01)	6.04 (6.01, 12.01)
T>Bas (h)	209.493 (84.00, 264.01)	77.557 (0.00, 208.15)	215.768 (83.98, 263.99)	175.735 (80.01, 312.03)												
T<Bas (h)	102.552 (48.01, 227.93)	234.499 (104.03, 312.01)	96.257 (48.05, 228.07)	136.22 (0.00, 232.01)	23.920 (19.23, 24.15)	23.997 (23.93, 24.12)	23.941 (23.92, 23.95)	21.977 (8.98, 24.01)	23.921 (15.64, 23.96)	23.938 (23.93, 23.94)	23.947 (23.89, 23.95)	23.912 (19.46, 23.94)	72.004 (12.60, 72.07)	72.019 (66.02, 72.03)	72.060 (58.29, 72.09)	44.034 (6.03, 72.01)

Abbreviations: SAD, single ascending dose; MAD, multiple ascending doses; E_{max}, maximal effect; tE_{max}, time to maximal effect in serum uric acid; T>Bas, time interval during which the plasma concentration is above baseline; T<Bas, time interval during which the plasma concentration is below baseline.

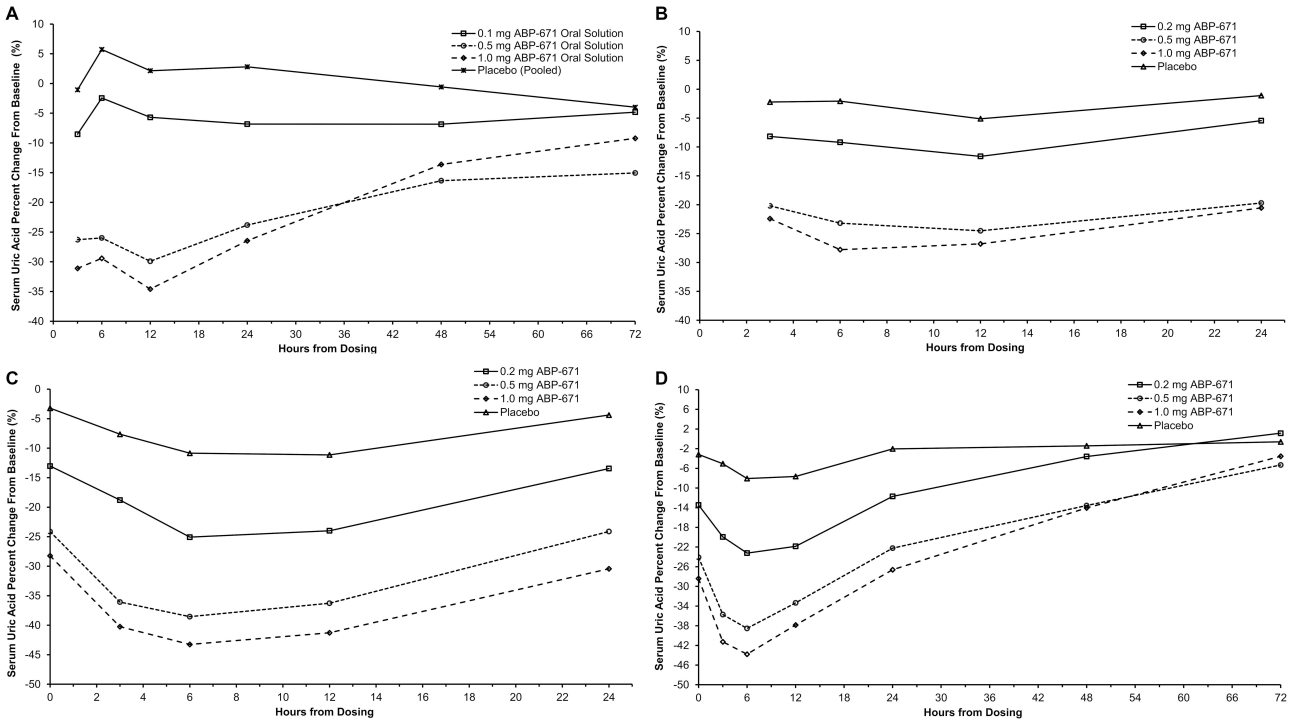

Figure 3 Percentage changes from baseline in serum uric acid (sUA) levels. (**A**) After a single dose of 0.1, 0.5, or 1.0 mg ABP-671 or placebo treatment in the single ascending dose (SAD) study. (**B**) Day 1 after administration of 0.2, 0.5, and 1.0 mg ABP-671 and placebo in the multiple ascending dose (MAD) study. (**C**) Day 5 after administration of 0.2, 0.5, and 1.0 mg ABP-671 and placebo in the MAD study. (**D**) Day 10 after administration of 0.2, 0.5, and 1.0 mg ABP-671 and placebo in the MAD study.

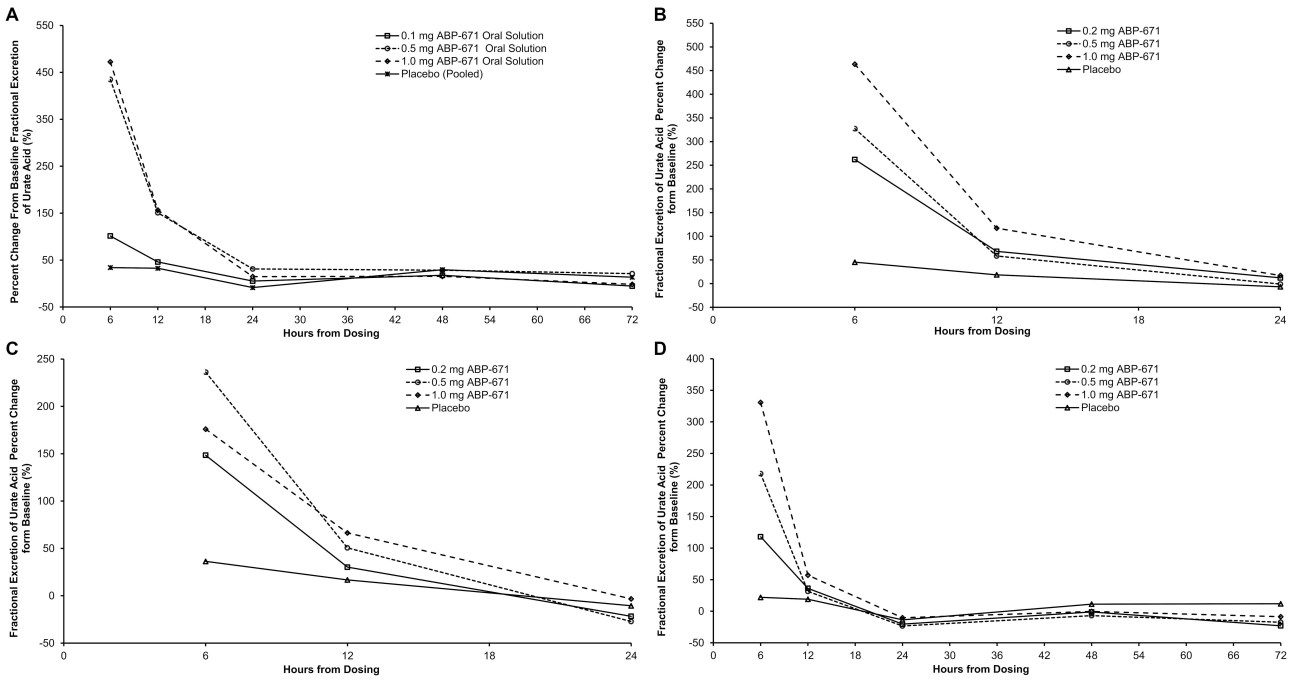

Figure 4 Percentage changes from baseline in uric acid (UA) fractional excretion. (**A**) After a single dose of 0.1, 0.5, or 1.0 mg ABP-671 or placebo treatment in the single ascending dose (SAD) study. (**B**) Day 1 after administration of 0.2, 0.5, or 1.0 mg ABP-671 or placebo 1 in the multiple ascending dose (MAD) study. (**C**) Day 5 after administration of 0.2, 0.5, or 1.0 mg ABP-671 or placebo in the MAD study. (**D**) Day 10 after administration of 0.2, 0.5, or 1.0 mg ABP-671 or placebo in the MAD study.

Table 5 Food Effects on PK and PD Parameters for the 1.0 mg Dose

Parameter	Fed	Fasted	GMR (90% CI), Fed/Fasted
C_{max} (ng/mL)	53.0±12.4	72.8±18.0	0.73 (0.68, 0.79)
AUC_{0-t} (h*ng/mL)	298±133	312±94.5	0.93 (0.87, 0.98)
AUC_{0-inf} (h*ng/mL)	322±144	329±95.0	0.95 (0.89, 1.01)
t_{max} (h)	2.75±0.962	1.21±0.401	-
$t_{1/2}$ (h)	4.86±1.43	4.99±1.37	-
Period 1 E_{max} (%)	−40.4±6.95	−38.3±16.3	-
Period 2 E_{max} (%)	−38.8±9.89	−35.8±7.71	-
Period 1 tE_{max} (h)	7.59±3.64	8.01±4.52	-
Period 2 tE_{max} (h)	8.26±2.97	7.01±2.44	-

Notes: Period 1: May 23, 2020-May 24, 2020; Period 2: May 27, 2020.
Abbreviations: GMR, geometric mean ratio; CI, confidence interval; AUC, area under the plasma concentration-time; C_{max}, peak plasma concentration; t_{max}, time to reach the peak plasma concentration following drug administration; $t_{1/2}$, half-life; E_{max}, maximal effect; tE_{max}, time to maximal effect in serum uric acid.

multiple oral doses of ABP-671 doses of 0.1 to 1mg up to 10 days are safe, tolerable, and rapidly absorbed. There is a proportional relationship between drug dose and plasma exposure. ABP-671 reduced the sUA levels with rapid onset, stable, and lasting effects. The fasting or postprandial state did not affect the PK of ABP-671. This was the first-in-human study to evaluate the safety, tolerability, PK, PD characteristics, and food effects of single and multiple oral doses of ABP-671.

Of note, URAT1 inhibitors are not recommended for subjects with kidney stones.[10,11] Increases in the rates of nephrolithiasis have also been reported with benzbromarone, a URAT1 inhibitor.[12] A Phase II study of verinurad (a URAT1 inhibitor) reported increases in serum creatinine in 17.1% of the subjects and no nephrolithiasis.[13] A study of

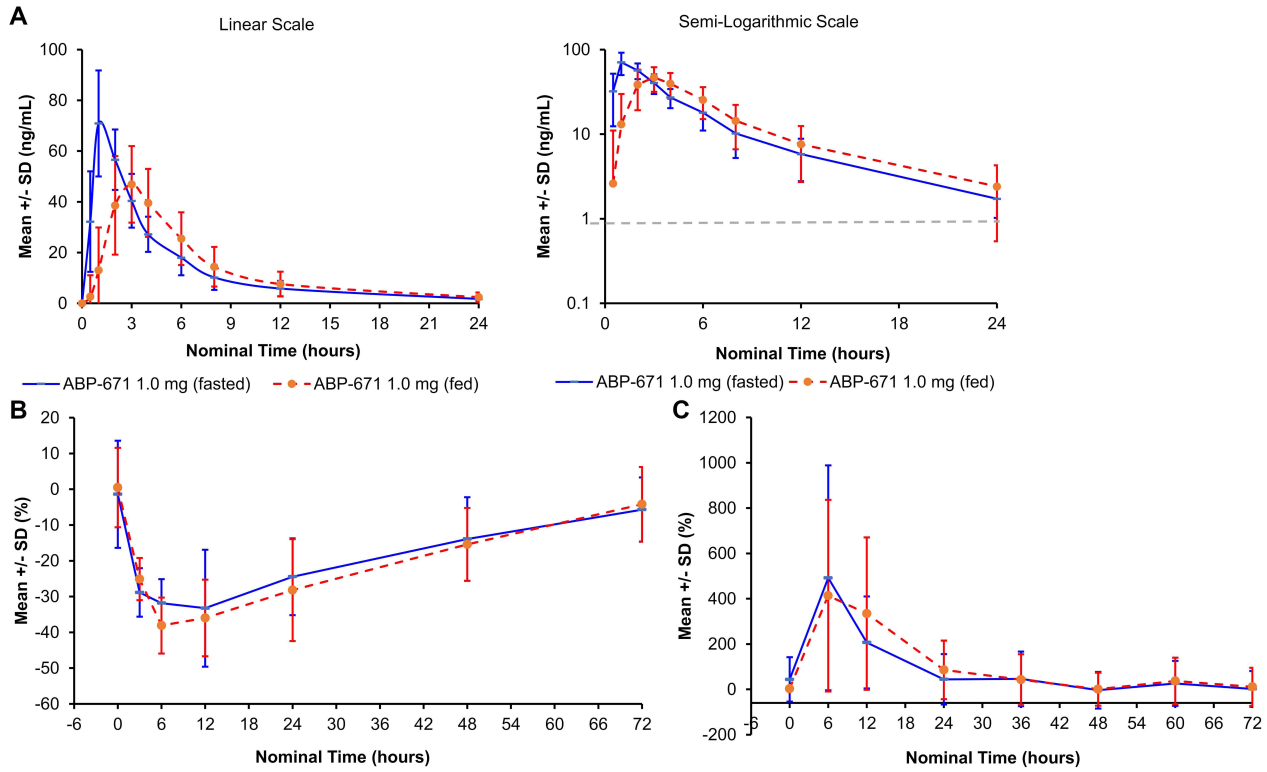

Figure 5 Food effects on the pharmacokinetic and pharmacodynamic parameters after a single dose of 1.0 mg ABP-671 in the fasted and fed states. (**A**) Plasma concentration time curves. (**B**) sUA percentage changes from baseline; (**C**) UA excretion rate.

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another URAT1 inhibitor, URC102, also reported TEAEs in 41% of the subjects.[14] The incidences of TEAEs in the dose groups in this study were low and, all events were mild to moderate. Across all dose groups in the SAD and MAD studies, the incidence of TEAEs ranged from 14% to 57%, which was comparable to the range observed in the placebo groups (13–33%). The most frequently reported TEAEs were gastrointestinal disorders, particularly diarrhea, which occurred in 17% (1/6) of subjects in the 0.1 mg SAD group, 14% (1/7) in the 0.5 mg MAD group, 14% (1/7) in the 1.0 mg MAD group, and 17% (1/6) in the MAD placebo group. In the food-effect cohort, diarrhea was reported in 8.3% (1/12) of subjects under both fasted and fed conditions. By contrast, other ULT drugs have been shown to lead to liver-related ADRs (adverse drug reactions) such as dotinurad, benzbromarone, and febuxostat.[15] Cardiac AEs were reported in a Phase I study of lesinurad.[16] These AEs were not observed in the present study with ABP-671. Furthermore, there were no SAEs or TEAEs leading to drug discontinuation, or TEAEs leading to death (similar to that observed with verinurad[17]), indicating that ABP-671 was well tolerated.

In the SAD and MAD studies, the C_{max} and AUCs of each dose group increased with increasing drug dose, and dose-proportional relationships were observed. Furthermore, t_{max} and $t_{1/2}$ were similar among the different dose groups. Similar results were reported with other URAT1 inhibitors currently in different phases of development including verinurad,[13] HR011303,[18] dotinurad (FYU-981),[19] arhalofenate (MBX-102),[20] UR-1102 (or URC-102),[21] and ABT-639.[9,22]

ABP-671 had a rapid onset of effect after administration (about 3 hours), and the maximum drug effect was reached within 24 h after administration. The PD parameters correlate well with drug dose. In the SAD study, ABP-671 at a dose of 1.0 mg resulted in a mean sUA reduction of 26% at 24 hours post-dose. In the MAD study, the same dose produced mean reductions ranging from 20% to 30% on Days 1, 5, and 10.

Of note, postprandial administration did not affect the exposure and efficacy of ABP-671, nor did it change the safety profile. This could be an advantage compared with verinurad, which showed delayed absorption with a moderate fat meal.[17] These results indicate that ABP-671 can be taken with or without a meal, facilitating its administration and improving dosing compliance.

This study has several limitations, including the small sample size and the short treatment duration, which may limit the generalizability of the findings and the assessment of long-term efficacy and safety.

Conclusion

Single and multiple oral doses of ABP-671 from 0.1 to 1mg up to 10 days were safe and tolerable, rapidly absorbed, and there was a proportional relationship between dose and exposure in human subjects. ABP-671 could significantly reduce the level of sUA in subjects with hyperuricemia, demonstrating a rapid onset of therapeutic effect. Further clinical trials are warranted to fully evaluate its therapeutic potential in patients with gout and hyperuricemia.

Data Sharing Statement

The data generated or analyzed in this study, including de-identified individual participant data, study protocols, and statistical analysis plans, may be available upon request, subject to sponsor approval. Requests will be reviewed for methodological rigor, and access will be granted for up to five years following publication. Inquiries should be directed to the corresponding author, who will coordinate with the sponsor.

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Author Contributions

All authors have made substantial contributions to the conception, design, execution, data acquisition, analysis, and interpretation of the study; have participated in drafting, revising, or critically reviewing the manuscript; have given final approval of the version to be published; have agreed on the target journal for submission; and accept responsibility for all aspects of the work to ensure its accuracy and integrity.

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