Effect of Food on the Pharmacokinetics of AND017 in a Phase I Study

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Background

- AND017 is a novel hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI) administered orally for treatment of patients with anemia due to chronic kidney disease (CKD).
- This phase I clinical trial was conducted to evaluate the effect of food on the pharmacokinetics (PKs) of AND017 in Chinese non-elderly healthy subjects. (NCT04712500)

Methods

Study Design

- Phase I, randomized, open-label, two-sequence, two-period, crossover study
- Eligible subjects were randomized in a 1:1 ratio to either Sequence A or Sequence B. Subjects received a single dose of 10 mg AND017 under fasted (Sequence A) or fed (Sequence B) conditions in the Period 1, followed by a 5-day washout period, and then another single dose of 10 mg AND017 under fed (Sequence A) or fasted (Sequence B) conditions in the Period 2 (**Figure 1**).

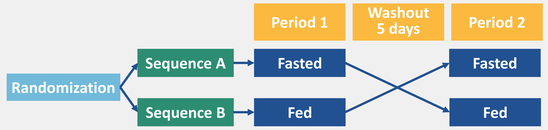

Figure 1. Study Design

Subjects

- Healthy male and female, age 18-45 years

Primary Objective

- To evaluate the food effect on the PKs ($AUC_{0\text{-}inf}$ and C_{max}) of single oral dose of AND017 at 10 mg

Secondary Objectives

- To evaluate the PKs of single oral dose of AND017 at 10 mg
- To evaluate the safety of single oral dose of AND017 at 10 mg

Results

Disposition and Demographics

- A total of 14 subjects were randomized with 7 subjects each in Sequence A and Sequence B.
- All 14 subjects completed both treatment periods with good compliance and were all included in the PK and safety analysis sets.
- The demographics of the subjects in the two sequences are shown in **Table 1.**

Results

Table 1. Demographics

Characteristics	Seq A N=7	Seq B N=7	Total N=14
Sex, n (%)			
Male	4 (57.1)	6 (85.7)	10 (71.4)
Female	3 (42.9)	1 (14.3)	4 (28.6)
Age (years)			
Mean	24.3	28.4	26.4
SD	2.4	5.5	4.6
Min, Max	21, 28	20, 36	20, 36
Weight (kg)			
Mean	60.1	63.6	61.9
SD	10.6	4.9	8.1
Min, Max	47.5, 77	55, 69.5	47.5, 77.0
BMI (kg/m^2)			
Mean	21.4	22.9	22.2
SD	1.7	1.9	1.9
Min, Max	19.3, 24.6	20.2, 25.9	19.3, 25.9

Table 2. Descriptive Statistics of PK Parameters

PK Parameters (unit)	Fed (N=14)		Fasted (N=14)	
	Mean (SD)	%CV	Mean (SD)	%CV
T_{max} (h), median (range)	4.5 (4.0-12.0)	45.02	4.0 (3.0-5.0)	17.40
C_{max} (ng/mL)	893 (124)	13.89	1125 (182)	16.16
$AUC_{0\text{-}t}$ (ng·h/mL)	19236 (4460)	23.19	19244 (4639)	24.10
$AUC_{0\text{-}inf}$ (ng·h/mL)	20297 (5057)	24.91	20355 (5216)	25.63
λ_z (h^{-1})	0.05 (0.01)	16.79	0.05 (0.01)	23.03
$t_{1/2}$ (h)	15.5 (2.9)	18.77	16.2 (4.2)	25.55
Vz/F (mL)	11333 (2023)	17.85	11775 (2498)	21.21
CL/F (mL/h)	521 (124)	23.84	522 (130)	24.87
$\%AUC_{ex}$	4.8 (2.9)	61.18	5.0 (3.3)	64.97
$AUC_{0\text{-}24}$ (ng·h/mL)	12612 (2008)	15.92	13174 (2565)	19.47

PK Analysis

- Compared to fasted conditions, AND017 administered under fed conditions showed a lower C_{max} and a delayed T_{max} (**Table 2**).
- All other PK parameters showed no obvious differences between fed and fasted states (**Table 2**).
- The half-life of single dose 10 mg AND017 was around 15.5–16.2 h, and T_{max} was around 4.0–4.5 h (**Table 2**).
- Bioavailability analysis indicated no significant difference in $AUC_{0\text{-}inf}$ between fed and fasted states (**Table 3**).
- C_{max} was reduced by approximately 20% under fed conditions compared to the fasted condition (**Table 3**).
- In the ANOVA analysis, study period and sequence group were found to have no effect on log-transformed C_{max} and $AUC_{0\text{-}inf}$ (**Table 4**).

Table 3. Bioavailability Variables

Parameters (unit)	Geometric Mean and Ratio				Power (%)
	Fed (N=14) GM	Fasted (N=14) GM	Fed/Fasted (%)	90% CI (%)	
C_{max} (ng/mL)	885.21	1111.98	79.61	(73.40, 86.34)	4.03
$AUC_{0\text{-}inf}$ (ng·h /mL)	19732.00	19746.40	99.93	(96.31, 103.68)	100.00

Table 4. ANOVA for Primary PK Parameters

Main Factors	P-value (N=14)	
	LnC_{max}	$LnAUC_{0\text{-}inf}$
Dosing Sequence	0.177	0.020
Dosing Period	0.986	0.285
Dosage form	<0.001	0.972

Safety Analysis

- A total of 7 subjects (50.0%) experienced adverse events (AEs), all of which occurred after dosing, and were therefore treatment-emergent AEs (TEAEs) (**Table 5**).
- The frequently reported TEAEs (>5%) were C-reactive protein increased (14.3%) and fear of injection (14.3%), each occurred in 2 subjects (**Table 6**).
- A total of 3 subjects (21.4%) experienced TEAEs deemed treatment-related (**Table 5**), which were alanine aminotransferase increased (7.1%), blood pressure diastolic decreased (7.1%), blood triglycerides increased (7.1%), blood creatine phosphokinase increased (7.1%).
- All TEAEs were mild or moderate with CTCAE grade 1 or 2. No serious AEs (SAEs) or AEs leading to discontinuation occurred in the study (**Table 5**).

Table 5. Summary of AEs

Adverse Events n (%)	Total N=14
Any AE	7 (50.0)
Any TEAE	7 (50.0)
Any treatment-related TEAE	3 (21.4)
Any TEAE with CTCAE grade≥3	0
Any SAE	0
Any AE leading to discontinuation	0

Table 6. Summary of TEAEs

Adverse Events n (%)	Total N=14
Any TEAE	7 (50.0)
C-reactive protein increased	2 (14.3)
Fear of injection	2 (14.3)
Alanine aminotransferase increased	1 (7.1)
Blood pressure diastolic decreased	1 (7.1)
Blood triglycerides increased	1 (7.1)
Blood creatine phosphokinase increased	1 (7.1)
Blood uric acid increased	1 (7.1)
Abdominal pain	1 (7.1)
Sinus bradycardia	1 (7.1)

Conclusion

- The current formulation of AND017 can be administered with or without food.
- A single dose of 10 mg AND017, whether administered alone or with food, was generally safe and well-tolerated in healthy, non-elderly subjects.

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For more information, please contact by email yushazhu@kindpharmaceutical.com or visit www.kindpharmaceuticals.com

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