First-in-Human Study of Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI) AND017 in Healthy Participants

Yusha Zhu[1], Ping Du[1], Qi Zhu[1]

[1]Kind Pharmaceuticals LLC, Redwood City, CA, USA

KIND PHARMACEUTICAL

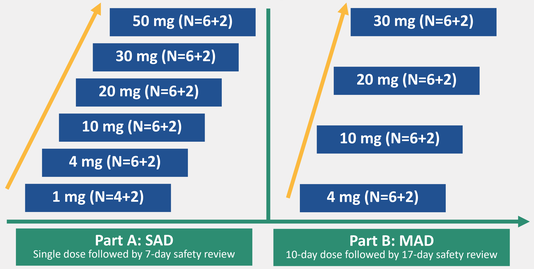
Background

- 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 in Australia to evaluate the pharmacokinetics (PKs), pharmacodynamics (PDs) and safety of AND017 among healthy subjects. (NCT04751539)

Methods

Study Design

- Phase I, randomized, double-blinded, placebo-controlled study
- The study consisted of two parts: Part A single ascending dose (SAD) phase, followed by Part B multiple ascending dose (MAD) phase (**Figure 1**).



❖ N=x+y, x- AND017, y- placebo; SAD – Single ascending dose; MAD – Multiple ascending dose;

Figure 1. Study Design

Subjects

- Healthy male and female, age 18-45 years

Primary Objective

- To evaluate the safety and tolerability of AND017 following single and multiple oral doses

Secondary and Exploratory Objective

- To characterize the PKs of AND017 in plasma
- To evaluate the PD response of AND017

Results

Disposition and Demographics

- A total of 78 subjects were enrolled with 46 in Part A SAD phase and 32 in Part B MAD phase.
- All subjects were included in the PD and safety analysis set; all 58 subjects received AND017 were included in the PK analysis set.
- Subjects in all treatment groups were of similar demographics and baseline characteristics. In Part A, the mean age was 25.2 years, and 41.3% was female; in part B, the mean age was 29.7 years and 50% was female.

Results

Safety Analysis

- In Part A, 15 subjects (32.6%) experienced treatment-emergent adverse events (TEAEs), among which 12 subjects were dosed with AND017 (35.3%) (**Table 1**).
- The frequently reported TEAEs (>5%) in the pooled AND017 group were dizziness (14.7%), fatigue (11.8%), and headache (8.8%) (**Table 1**).

Table 1. Summary of TEAEs in Part A SAD Phase

Adverse Events n (%)	Pooled AND017 N=34	Placebo N=12
Any TEAE	12 (35.3%)	3 (25.0%)
Dizziness	5 (14.7%)	0
Fatigue	4 (11.8%)	1 (8.3%)
Headache	3 (8.8%)	0
Constipation	1 (2.9%)	0
Flatulence	1 (2.9%)	0
Tongue discomfort	1 (2.9%)	0
Cough	1 (2.9%)	0
Dyspnea	1 (2.9%)	0
Neck pain	1 (2.9%)	0
Rash	1 (2.9%)	0
Toothache	0	1 (8.3%)
Nasal congestion	0	1 (8.3%)
Oropharyngeal pain	0	1 (8.3%)

- In Part B, 16 subjects (50.0%) experienced TEAEs, among which 10 subjects were dosed with AND017 (41.7%) (**Table 2**).
- The most frequently reported AE (>5%) in the pooled AND017 group was headache (12.5%) (**Table 2**).
- No SAEs, deaths, or AEs leading to discontinuation in both study parts.

Table 2. Summary of TEAEs in Part B MAD Phase

Adverse Events n (%)	Pooled AND017 N=24	Placebo N=8
Any TEAE	10 (41.7%)	6 (75.0%)
Headache	3 (12.5%)	2 (25.0%)
Dysmenorrhea	1 (4.2%)	2 (25.0%)
Erythema	1 (4.2%)	1 (12.5%)
Acne	1 (4.2%)	0
Dermatitis	1 (4.2%)	0
Change of bowel habit	1 (4.2%)	0
Dyspepsia	1 (4.2%)	0
Skin injury	1 (4.2%)	0
Skin laceration	1 (4.2%)	0
Seasonal allergy	1 (4.2%)	0
Rhinitis	1 (4.2%)	0
Back pain	1 (4.2%)	0
Nightmare	1 (4.2%)	0
Hyperhidrosis	0	1 (12.5%)
Diarrhea	0	1 (12.5%)
Chest pain	0	1 (12.5%)

PK Analysis

- The PK profiles in Part A and Part B were comparable.
- There was no tendency toward a change in T_{max}, half-life, volume of distribution, and clearance across the dose range investigated in the SAD and MAD phases (**Table 3-5**).
- The median T_{max} ranged from 2.0-4.5 h and the mean half-life ranged from 10.1-19.7 h after single and multiple dose administration (**Table 3-5**).

Table 3. Plasma AND017 PK Parameters on Day 1 in Part A SAD Phase

PK Parameters Mean (SD)	1 mg N=4	4 mg N=6	10 mg N=6	20 mg N=6	30 mg N=6	50 mg N=6
T_{max} (h), median	3.0	3.0	3.0	4.5	3.0	3.0
C_{max} (ng/mL)	83 (43)	412 (204)	969 (360)	1759 (891)	4040 (831)	5987 (2569)
$AUC_{0\text{-}inf}$ (ng·h/mL)	986 (267)	5424 (2397)	13873 (5218)	22187 (7581)	59150 (23861)	80447 (33997)
$t_{1/2}$ (h)	19.7 (3.2)	14.7 (3.1)	13.4 (1.3)	13.1 (2.2)	15.9 (5.2)	11.9 (1.0)
V_z/F (L)	31.0 (10.8)	18.4 (7.8)	15.1 (4.2)	17.9 (3.8)	12.0 (1.8)	12.7 (6.6)
CL/F (L/h)	1.1 (0.2)	0.9 (0.4)	0.8 (0.2)	1.0 (0.3)	0.6 (0.2)	0.7 (0.3)

Table 4. Plasma AND017 PK Parameters on Day 1 in Part B MAD Phase

PK Parameters Mean (SD)	4 mg N=6	10 mg N=6	20 mg N=6	30 mg N=6
T_{max} (h), median	2.5	3.0	2.0	2.0
C_{max} (ng/mL)	374 (86)	741 (177)	1642 (349)	2893 (810)
$AUC_{0\text{-}inf}$ (ng·h/mL)	4553 (1555)	9134 (2473)	19654 (1887)	55881 (15466)
$t_{1/2}$ (h)	12.7 (7.5)	10.1 (1.4)	10.6 (1.5)	19.4 (10.9)
V_z/F (L)	15.3 (3.2)	16.7 (4.0)	15.5 (2.1)	14.5 (4.4)
CL/F (L/h)	1.0 (0.3)	1.2 (0.3)	1.0 (0.1)	0.6 (0.2)

Table 5. Plasma AND017 PK Parameters on Day 10 in Part B MAD Phase

PK Parameters Mean (SD)	4 mg N=6	10 mg N=6	20 mg N=6	30 mg N=6
$T_{ss,max}$ (h), median	3.5	3.0	3.0	4.0
$C_{ss,avg}$ (ng/mL)	197 (50)	477 (122)	814 (173)	1771 (565)
$AUC_{0\text{-}inf}$ (ng·h/mL)	7171 (3090)	16205 (4230)	26666 (7722)	63785 (31272)
$t_{1/2}$ (h)	15.8 (3.4)	14.1 (1.0)	12.4 (2.2)	13.5 (4.4)
V_{ss}/F (L)	19.6 (2.7)	18.7 (4.7)	18.6 (2.4)	13.8 (1.5)
CL_{ss}/F (L/h)	0.9 (0.2)	0.9 (0.2)	1.1 (0.3)	0.8 (0.2)
DF (%)	187 (54)	172 (40)	174 (20)	138 (45)
R_{ac} (AUC)	1.5 (0.3)	1.6 (0.1)	1.3 (0.3)	1.3 (0.5)
R_{ac} (C_{max})	1.3 (0.4)	1.4 (0.2)	1.2 (0.4)	1.3 (0.6)

- PK analysis in Part B MAD phase showed that AND017 plasma concentration reached steady state on Day 6 after once-daily dosing.
- There was an approximate 1.2-1.6-fold accumulation after 10 consecutive days of administration.
- Dose proportionality was confirmed with the regression slope close to 1, indicating a proportional increase in exposure across the investigated dose range.

PD Analysis

- The PD parameters of EPO in Part A SAD phase, on Day 1 and Day 10 in the Part B MAD phase showed obvious dose dependence.
- In Part A SAD phase, EPO levels showed a marked increase from baseline at 6 h post-dose in the AND017 20 mg, 30 mg, and 50 mg groups, with a peak observed around 12 h post-dose.
- In Part B MAD phase, EPO showed an obvious increase from baseline at 6 h post-dose in the AND017 high dose groups (20 mg and 30 mg) (**Figure 2**).
- In the PK/PD relationship analysis, the increases in EPO parameters were significantly associated with AND017 PK exposures.

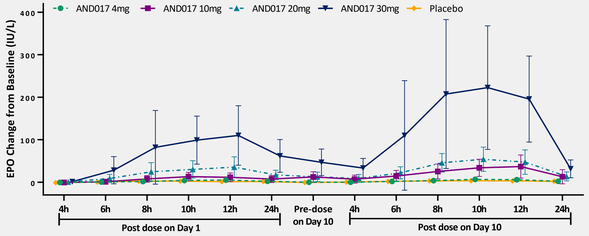


Figure 2. Line Plot of Change from Baseline in EPO in Part B MAD Phase

- The PD parameter Hb was assessed in Part B MAD phase. High dose levels of AND017 (20 mg and 30 mg) showed greater mean of change from baseline in Hb levels (**Figure 3**).
- Similar results were observed in the PD parameters red blood cell and absolute reticulocyte count.

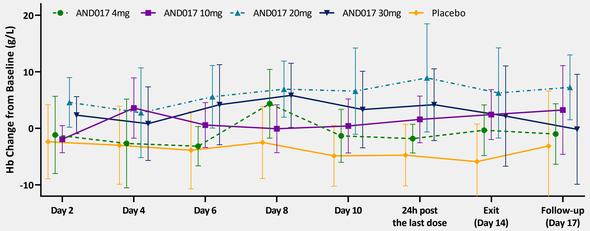


Figure 3. Line Plot of Change from Baseline in Hb in Part B MAD Phase

Conclusion

- AND017 was safe and well tolerated in healthy adult subjects at single oral doses ranging from 1 mg to 50 mg, as well as at multiple doses of 4 mg to 30 mg administered over 10 consecutive days.

KIDNEY WEEK 2024

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

Poster Board: TH-PO896 October 24, 2024