Safety and Efficacy of AND017, a Hypoxia Inducible Factor-Prolyl-Hydroxylase Inhibitor (HIF-PHI) in Patients with Non-Dialysis-Dependent CKD (NDD-CKD)

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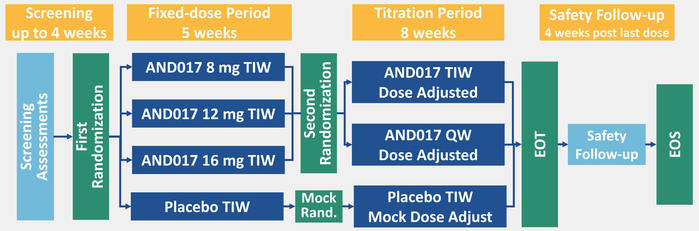
Background

- 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 II clinical trial was conducted in the US and China to evaluate the safety and efficacy of AND017 among patients with non-dialysis-dependent CKD (NDD-CKD). (NCT05035641)

Methods

Study Design

- Phase II, randomized, double-blinded, placebo-controlled, dose ranging study
- The study consisted of two treatment periods: a 5-week fixed-dose period followed by an 8-week titration period, during which dose adjustments based on Hb levels were allowed. Qualified patients were randomized at 1:1:1:1 to one of the treatment groups to receive AND017 at various doses or placebo three times per week (TIW) for a 5-week treatment, and re-randomized at Week 6 to enter the 8-week Titration Period (**Figure 1**).



❖ ESA – Erythropoietin stimulating agents; EOT – End of treatment; EOS - End of study

Figure 1. Study Design

Eligibility

- Age ≥ 20 years
- Not receiving dialysis with eGFR < 60 mL/min/1.73 m^2
- Hb ≥7.5 g/dL and <10.0 g/dL

Primary Objectives

- To evaluate the safety and tolerability of AND017 following various dosing regimens
- To compare the rate of rise in Hb for AND017 doses with placebo from baseline to 5 weeks after TIW oral dosing

Results

Disposition and Demographics

- A total of 113 patients were enrolled in the study, with 28, 28, 29, and 28 patients in the placebo, AND017 8 mg, 12 mg, and 16 mg dose groups, respectively.
- All 113 patients were included in the safety analysis set; 109 patients received at least one dose of AND017/placebo and had at least one post-dose efficacy Hb level were included in the full analysis set for primary efficacy analysis.
- Patients in all treatment groups were of relatively similar demographic and baseline characteristics (mean age 59.6 years, 66.4% female, 68.1% Asian, 11.5% African American, 19.5% White, mean baseline Hb 9.15 g/dL, mean baseline eGFR 20.14 mL/min/1.73 m^2).

Results

Primary Efficacy Analysis

- The primary endpoint was to compare the rate of rise in Hb for AND017 doses with placebo from baseline to 5 weeks after TIW oral dosing.
- The ANCOVA model was used as the primary analysis model (**Table 2**), and the MMRM was the sensitivity analysis model (**Table 3**).
- Both models showed that the mean rate of rise in Hb from baseline to Week 6 was significantly higher in all the AND017 dose groups compared to the placebo group (**Table 2** and **Table 3**).
- In a correlation analysis, the dose of AND017 and the rate of rise in Hb was linearly correlated, with a Pearson correlation coefficient 0.72 in a linear regression model.

Table 1. Hb Levels and Change from Baseline in Hb Levels at Week 6

Hb Levels (g/dL)	Placebo N=28	AND017 8 mg N=27	AND017 12 mg N=27	AND017 16 mg N=27
Hb at Week 6, Mean (SD)	9.04 (0.90)	10.52 (1.30)	11.06 (1.00)	11.75 (1.17)
Hb change from baseline, Mean (SD)	-0.21 (0.57)	1.44 (1.02)	2.03 (0.77)	2.51 (1.20)

Table 2. Rate of Rise in Hb by ANCOVA Model

Rate of Rise in Hb (g/dL/week)	Placebo N=28	AND017 8 mg N=27	AND017 12 mg N=27	AND017 16 mg N=27
Mean (SD)	-0.04 (0.09)	0.28 (0.19)	0.39 (0.20)	0.48 (0.24)
AND017 VS Placebo, ANCOVA model				
LS mean (95% CI)	-0.04 (-0.11, 0.04)	0.28 (0.21, 0.36)	0.39 (0.31, 0.46)	0.48 (0.41, 0.56)
LS mean diff. (95% CI)		0.32 (0.20, 0.44)	0.42 (0.30, 0.55)	0.52 (0.40, 0.64)
P-value		<.0001	<.0001	<.0001

Table 3. Rate of Rise in Hb by MMRM Model

Rate of Rise in Hb (g/dL/week)	Placebo N=28	AND017 8 mg N=27	AND017 12 mg N=27	AND017 16 mg N=27
Week 2 LS mean (95% CI)	-0.05 (-0.15, 0.05)	0.13 (0.03, 0.24)	0.10 (-0.01, 0.20)	0.24 (0.14, 0.34)
Week 3 LS mean (95% CI)	-0.03 (-0.11, 0.04)	0.17 (0.10, 0.24)	0.28 (0.20, 0.35)	0.37 (0.30, 0.44)
Week 4 LS mean (95% CI)	-0.06 (-0.13, 0.01)	0.19 (0.12, 0.26)	0.31 (0.24, 0.39)	0.36 (0.29, 0.43)
Week 5 LS mean (95% CI)	-0.02 (-0.08, 0.03)	0.21 (0.16, 0.27)	0.32 (0.26, 0.38)	0.40 (0.34, 0.45)
Week 6 LS mean (95% CI)	-0.04 (-0.10, 0.02)	0.24 (0.18, 0.30)	0.32 (0.25, 0.38)	0.43 (0.37, 0.49)
AND017 VS Placebo, MMRM model				
Week 6 LS mean diff. (95% CI)		0.28 (0.19, 0.37)	0.36 (0.27, 0.44)	0.47 (0.38, 0.56)
P-value		<.0001	<.0001	<.0001

- The cumulative response rate, defined as the percentage of patients had an Hb ≥10.0 g/dL and increase from baseline for ≥1.0 g/dL during the entire treatment period, were higher in all AND017 dose and dosing frequency groups than the placebo group (**Table 4**).

Table 4. Treatment Differences in Cumulative Response Rate

	Placebo N=5	AND017 TIW				AND017 QW			
		8 mg N=5	12 mg N=8	16 mg N=6	Pooled TIW N=19	8 mg N=6	12 mg N=8	16 mg N=6	Pooled QW N=20
Cum. response rate n (%)	2 (40.00)	5 (100)	8 (100)	6 (100)	19 (100)	5 (83.33)	8 (100)	5 (83.33)	18 (90.00)
AND017 VS Placebo									
Relative diff. (95% CI)		60.00 (0.15, 88.96)	60.00 (14.00, 88.79)	60.00 (5.62, 88.89)	60.00 (22.57, 88.53)	43.33 (-16.06, 80.52)	60.00 (14.00, 88.79)	43.33 (-16.06, 80.52)	50.00 (8.02, 81.38)

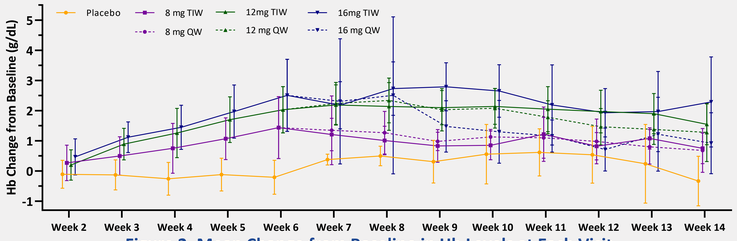


Figure 2. Mean Change from Baseline in Hb Levels at Each Visit

Safety Analysis

- Treatment emergent adverse events (TEAEs) occurred in 59 patients (69.4%) in the pooled AND017 group and 18 patients (64.3%) in the placebo group (**Table 5**).
- The treatment-related TEAEs occurred in 10 patients (11.8%) in the pooled AND017 group and 1 patient (3.6%) in the placebo group.
- A total of 6 patients, 3 of AND017 12 mg group and 3 of AND017 16 mg group, experienced serious AEs (SAEs), none of which were assessed as treatment related.

Table 5. Summary of TEAEs with Incidence >5% in Any Treatment Group

Adverse Events n (%)	AND017 8 mg N=28	AND017 12 mg N=29	AND017 16 mg N=28	Pooled AND017 N=85	Placebo N=28
Any TEAE	14 (50.0%)	22 (75.9%)	23 (82.1%)	59 (69.4%)	18 (64.3%)
Hyperkalaemia	3 (10.7%)	4 (13.8%)	3 (10.7%)	10 (11.8%)	3 (10.7%)
Hyperphosphatemia	3 (10.7%)	2 (6.9%)	4 (14.3%)	9 (10.6%)	1 (3.6%)
Upper respiratory tract infection	5 (17.9%)	1 (3.5%)	1 (3.6%)	7 (8.2%)	1 (3.6%)
Dizziness	1 (3.6%)	2 (6.9%)	3 (10.7%)	6 (7.1%)	0
Headache	2 (7.1%)	3 (10.3%)	1 (3.6%)	6 (7.1%)	0
Hypertension	1 (3.6%)	0	5 (17.9%)	6 (7.1%)	1 (3.6%)
Hyperlipidaemia	1 (3.6%)	0	3 (10.7%)	4 (4.7%)	0
Pneumonia	1 (3.6%)	1 (3.5%)	2 (7.1%)	4 (4.7%)	0
COVID-19	0	1 (3.5%)	2 (7.1%)	3 (3.5%)	1 (3.6%)
Hyperuricaemia	0	0	2 (7.1%)	2 (2.4%)	1 (3.6%)
Gout	0	0	2 (7.1%)	2 (2.4%)	0
Oedema peripheral	0	1 (3.5%)	1 (3.6%)	2 (2.4%)	2 (7.1%)
Diarrhoea	0	2 (6.9%)	0	2 (2.4%)	0

Conclusion

- AND017 was safe and well tolerated in NDD-CKD patients with similar safety profile as the placebo.
- AND017 effectively increased the Hb level in a dose-dependent manner starting at 8 mg TIW within the first 5-week fixed-dose period.
- The Hb levels were maintained within the target range 10.0-11.0 g/dL at both TIW and QW dosing frequency in the following 8-week titration period.

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

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