CLINICAL STUDY REPORT Synopsis

No: KHB-1802

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Study Title Short Study Title:	A Multicenter, Double-Masked, Randomized,Dose-Ranging Trial to Evaluate the Efficacy and Safety of Conbercept Intravitreal Injection in Subjects with Neovascular Age-related Macular Degeneration Safety of Conbercept		
Sponsor:	Chengdu Kanghong Biotechnology Co., Ltd.		
Protocol no:	KHB-1802	**Development phase:**	3
Study period:	From: December 21, 2018 To: May19, 2021	**Early termination of the study:**	YES ☑ NO ☐
Investigational product:	Conbercept, a biologic that functions as a VEGF-antagonist		
Indication:	Neovascular Age-Related Macular Degeneration		
Earlier report from the same study:	None	**Archiving:**	NA
Date of report:	January 18, 2023	**Author:**	Lin Song

Company/Sponsor Signatory:
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This study was conducted in compliance with Good Clinical Practice [GCP], including the archiving of essential documents

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Name of Sponsor: Chengdu Kanghong Biotechnology Co., Ltd.	
Name of Investigational Product: Conbercept	
Name of Active Ingredient: Conbercept is a fusion protein consisting of VEGFR1 (d2) and VEGFR2 (d3 and d4) regions fused to human IgG1 Fc.	
Title of Study: A Multicenter, Double-Masked, Randomized, Dose Ranging Trial to Evaluate the Efficacy and Safety of Conbercept Intravitreal Injection in Subjects with Neovascular Age-Related Macular Degeneration	
Protocol Number: KHB-1802	
Publication (reference): NA	
Study Period: Date of first enrolment: December 21, 2018 Date of last completed: May 19, 2021	**Phase of Development:** Phase 3
Objectives: The primary endpoint of the study were: The mean change from baseline in BCVA at Week 36. Secondary endpoints: • Proportion of subjects maintaining vision from baseline to Week 36; • Proportion of subjects gaining at least 15 ETDRS BCVA letters from baseline to Week 36; • The mean change from baseline in retinal thickness at Week 36; • Proportion of subjects maintaining vision from baseline to Week 48; • The mean change from baseline in BCVA at Week 96; • Safety, tolerability, pharmacokinetics and immunogenicity.	
Methodology: This is a multicenter, double-masked, parallel-group, dose-ranging, active-controlled, randomized clinical trial.	
Number of Subjects : The study planned to randomize approximately 1140 subjects in a ratio of 1:1:1 to receive IVT injections of 0.5 mg Conbercept, 1.0 mg Conbercept, or 2.0 mg Aflibercept.	
Diagnosis and Main Criteria for Inclusion and Exclusion: **Inclusion Criteria:** 1. Men and women ≥ 50 years of age at the Screening visit; 2. Females must be at least 1 year postmenopausal, or surgically sterilized, or, if of childbearing potential, must have a negative pregnancy test at the Screening visit; ○ Women of childbearing potential must agree to use a highly effective method of contraception throughout the study (See complete list in the Study Procedures Manual); 3. Have received no previous treatment for neovascular AMD, including laser photocoagulation and/or photodynamic therapy (PDT) and/or IVT VEGF antagonists (treatment naïve) and; 4. Have active subfoveal CNV lesions secondary to AMD (including polypoidal choroidal	

asculopathy (PCV)) evidenced by subfoveal FA leakage, or definite subfoveal fluid by SD-OCT in the study eye at Screening;

5. Have CNV that is at least 50% of total lesion size in the study eye at Screening;
6. Have a ETDRS BCVA letter score of 78 to 25 (approximately 20/32 to 20/320 equivalent) in the study eye at Screening;
7. Have ocular media (lens, cornea, vitreous) of adequate clarity to permit high quality fundus imaging;
8. Are willing and able to sign the study written informed consent form (ICF).

Exclusion Criteria:

1. Have had any prior ocular or systemic treatment (investigational or approved) or surgery for the treatment of neovascular AMD in the study eye except dietary supplements or vitamins;
2. Have participated as a subject in any interventional clinical trial within one month (30 days) prior to Baseline visit;
3. Have a total lesion size greater than twelve disc areas (30.5 mm^2), including blood, fibrosis and neovascularization, as assessed by FA in the study eye at Screening;
4. Have a subretinal hemorrhage that is either 50% or more of the total lesion area, or blood is under the fovea and is one or more disc areas in size (greater than 2.5 mm^2) in the study eye at Screening;
5. Have scarring or fibrosis making up greater than 50% of total lesion in the study eye at Screening; and/or scarring, fibrosis or atrophy involving the center of the fovea in the study eye at Screening;
6. Have any retinal pigment epithelial tears or rips in the study eye at Screening or upon examination at Baseline;
7. Have any vitreous hemorrhage in the study eye upon examination at Baseline or history of vitreous hemorrhage within eight weeks prior to Screening;
8. Have any other cause of CNV, including pathologic myopia (defined per protocol as spherical equivalent of -8 diopters or more), ocular histoplasmosis syndrome, angioid streaks, inherited macular dystrophies, choroidal rupture, uveitis, punctate inner choroidopathy, or multifocal choroiditis in the study eye at Screening;
9. Have a history of or clinical evidence of significant diabetic retinopathy that could impact assessment of vision or affect central vision, diabetic macular edema, or any other vascular disease other than AMD including history or clinical evidence of retinal vein occlusion affecting the study eye at Screening;
10. Have had prior pars plana vitrectomy in the study eye;
11. Have presence of a full thickness macular hole at Screening or upon examination at Baseline or a history of a full thickness macular hole in the study eye;
12. Have a history of intraocular or periocular surgery within three months of Baseline in the study eye, except in the case of lid surgery, which may not have taken place within one month of Baseline as long as it is unlikely to interfere with IVT injection;
13. Have prior trabeculectomy or other filtration surgery in the study eye;
14. Have uncontrolled glaucoma (defined as intraocular pressure (IOP) greater than or equal to 22 mmHg at Baseline despite treatment with more than two anti-glaucoma medications) in the study eye;
15. Have active intraocular inflammation in either eye at Screening or upon examination at

Baseline or a history of uveitis in either eye;

16. Have active ocular or periocular infection in either eye, or a history of any ocular or periocular infection within the two weeks prior to Screening in either eye;
17. Have presence or history of scleromalacia in either eye;
18. Have aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of yttrium aluminum garnet (YAG) posterior capsulotomy) in the study eye;
19. Have had previous therapeutic radiation in the region of the study eye;
20. Have history of corneal transplant or presence of a corneal dystrophy that interferes with IOP measurements or imaging in the study eye;
21. Significant media opacities, including cataract, in the study eye that, in the opinion of the Investigator, could require either medical or surgical intervention during the study period;
22. Have any concurrent ocular condition in the study eye that, in the opinion of the Investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or that otherwise may interfere with the injection procedure or with evaluation of efficacy or safety during the study;
23. Have any evidence by medical history, physical examination or clinical laboratory testing at Screening or Baseline that shows reasonable suspicion of a disease or condition that contraindicates the use of study medication (Conbercept or Aflibercept) or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications;
24. Have any use of long acting intraocular steroids, including implants, within six months prior to Day 1, Baseline;
25. Have any known allergy to povidone iodine or known serious allergy to the fluorescein sodium for injection in angiography;
26. Any history of known contraindications indicated in the Food and Drug Administration (FDA)-approved label for the active control;
27. If female, be pregnant (positive urine pregnancy test at Screening) or breastfeeding.

Test Product, Dose, and Mode of Administration:

IVT injections of 0.5 mg Conbercept, 1.0 mg Conbercept.

Subjects randomized to the Conbercept treatment arms will receive an IVT injection of either 0.5 mg or 1.0 mg Conbercept at 4-week intervals on Day 1, Week 4 and Week 8 (loading phase).

Subjects in the Conbercept treatment 0.5 mg arm will begin dosing every 8 weeks (q8w) after the first three injections through Week 36. At the Week 40 visit, the criteria-based PRN approach will begin through the end of the treatment period at Week 92 ;

Subjects in the Conbercept treatment 1.0 mg arm will begin dosing every 12 weeks (q12w) after the first three injections through Week 36. At the Week 40 visit, the criteria-based PRN approach will begin through the end of the treatment period at Week 92.

Reference Therapy, Dose, and Mode of Administration:

IVT injections of 2.0 mg Aflibercept.

Subjects randomized to the Aflibercept will be dosed as an IVT injection on Day 1, Week 4 and Week 8 and every 8 weeks (q8w) thereafter through Week 36. At the Week 40 visit, the criteria-based PRN approach will begin through the end of the treatment period at Week 92.

Statistical Methods:

The adverse factors caused by the global outbreak of COVID-19 and changes in the external environment have affected the quality of the trial. It was impossible to perform scientific objective analysis based on the expected goals of the clinical trials. After commercial consideration, the company has decided to discontinue the PANDA studies.

All safety analyses will be performed on the safety population.The safety of Conbercept will be assessed primarily by the incidence of AEs. An AE will be considered a treatment-emergent AE (TEAE) if it occurs or worsens on or after initiation of treatment. An overall summary of TEAEs is presented including the number of events and the number of subjects with events (along with percentages) by treatment group for TEAEs.

Summary and Conclusions:

The adverse factors caused by the global outbreak of COVID-19 and changes in the external environment have affected the quality of the trial. It was impossible to perform scientific objective analysis based on the expected goals of the clinical trials. After commercial consideration, the company has decided to discontinue the PANDA studies.

Safety result:

All 1157 subjects enrolled in this study were included in safety analysis population (0.5mg Conbercept: 385 subjects; 1.0mg Conbercept: 386 subjects; 2.0mg Aflibecept: 386 subjects).

The total No. of TEAEs is 4169, which incurred in 82.63% of 1157 subjects. The subjects with TEAE accounted for 80.26%, 83.94% and 83.68% in the 0.5mg Conbercept, 1.0mg Conbercept and 2.0mg Aflibercept groups respectively. 12.36% of the subjects had TEAEs related to the treatment procedure, and the subjects with TEAEs related to the treatment procedure accounted for 0.5 mg, 1.0 mg Conbercept and 2.0 mg Aflibercept in the total number of subjects, respectively, 9.90%, 15.28% and 12.69%.

TEAEs leading to death occurred in 33 subjects(2.85%)of 1157 subjects, 3.38%, 1.81% and 3.37% of population respectively in the 0.5 mg, 1.0 mg Conbercept, and 2.0 mg Aflibercept group. However, all TEAEs leading to death were not related to treatment drugs and treatment procedures.

Safety conclusion:

Based on the safety data available for analysis, the result revealed conbercept has similar types of serious adverse events and ocular adverse events as aflibercept and as reported by other VEGF antagonists for IVT injection. In conclusion, conbercept is safe for subjects with nAMD.