Clinical Study Protocol

Protocol Title: A Phase III, Randomized, Multicenter, Doubled-blind clinical trial comparing the efficacy and safety of TAB014 and Lucentis® in neovascular age-related macular degeneration (nAMD) subjects

Protocol Number: TOT-CR-TAB014-III-01

Date of Protocol: December 08, 2022

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Protocol No.: TOT-CR-TAB014-III-01

Version： 1.3

Protocol Approval Signatures: Sponsor

I have read and approved this protocol. I agree to comply with all obligations of sponsor and all other pertinent requirements and guidelines for GCP set forth by applicable regulatory authorities and the ICH.

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Protocol Approval Signatures: Statistician

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Protocol Approval Signatures: Principal Investigator

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Name： Date：

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PROTOCOL UPDATE RECORDE

Version number	Main updated contents	Version Date
V1.0	Preliminary protocol	2020.12.03
V1.1	(1) addition of the analytical testing laboratory; (2) update of the statistical analysis responsible unit; (3) minor revisions to inclusion/exclusion/withdrawal criteria; and (4) modification of the immunogenicity positivity evaluation criteria	2021.03.03
V1.2	(1) Sponsor information revision; (2) Addition of BCVA as a stratification factor; (3) Revisions to inclusion/exclusion criteria, secondary endpoints, AESIs, immunogenicity patient selection, analysis populations, Phase 1 results, drug labeling, treatment suspension/termination, permitted delays, prohibited treatments, visit flowchart, procedure timeframes, post-injection visual assessment, unscheduled/ophthalmology visits, AEs/SUSARs, AE outcomes, pregnancy events, and aqueous humor cell grading.	2022.03.19
V1.3	(1) Revision/addition of the definition of CNV activity; (2) Update to the visit flowchart; (3) Revisions to inclusion/exclusion criteria; (4) Updates to medical history documentation; (5) Clarification of timeframe requirements for study procedures; (6) Specification of study eye selection criteria; (7) Revised criteria for termination indicators; (8) Updated guidance on pre-treatment antibiotic use; (9) Defined treatment intervals for the non-study eye; (10) Permitted treatment delays; and (11) Prohibited medications	2022.12.08

LIST OF ABBREVIATIONS

Abbreviation	Full Name
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
AMD	Age-related Macular Degeneration
AST	Aspartate Transaminase
APTT	Activated Partial Thromboplastin Time
BCVA	Best-corrected Visual Acuity
CF	Color Fundus
CRA	Clinical research associate
CNV	Choroidal Neovascularization
CRVO	Central Retinal Vein Occlusion
CRO	Contract Research Organization
CST	Central Subfield Thickness
CSR	Clinical study report
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFA	Fluorescein Fundus Angiography
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICGA	Indocyanine Green Angiography
ICH	The International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IOP	Intraocular pressure
IWRS	Interactive Web Response System

Abbreviation	Full Name
ME	Macular Edema
MedDRA	Medical Dictionary for Regulatory Activities
MIN	Minute
Nab	Neutralizing Antibody
NMPA	National Medical Products Administration
NIA	US National Institute on Aging
OCT	Optical Coherence Tomography
PCV	Polypoidal Choroidal Vasculopathy
PPS	Per Protocol Set
RCT	Randomized Controlled Trial
VA	Corrected Visual Acuity
VEGF	Vascular Endothelial Growth Factor
RAND	Randomized population Set
SAE	Serious Adverse Event
SUSAR	Serious Unexpected Suspected Adverse Reaction
SAP	Statistical Analysis Plan
SD	Spectral Domain
SD-OCT	Spectral Domain - Optical Coherence Tomography
SDV	Source Data Verification
SOC	System Organ Class
SS	Safety Set
PT	Preferred Term
TIA	Transient Ischemic Attac
nAMD	neovascular Age-related Macular Degeneration
WHO	World Health Organization
WHO Drug	World Health Organization Drug Dictionary

1 PROTOCOL SUMMARY& ASSESSMENT SCHEDUL

1.1 ROTOCOL SUMMARY

Protocol name	A Phase III, Randomized, Multicenter, Doubled-blind clinical trial comparing the efficacy and safety of TAB014 and Lucentis® in neovascular age-related macular degeneration (nAMD) subjects
Protocol Number	TOT-CR-TAB014-III-01
Clinical Trial number	2017L04523
Name of Sponsor	BIODLINK Biopharm Co., Ltd ZHAOKE(Guangzhou) Ophthalmology Pharmaceutical Co., Ltd.
Investigational drug	TAB014((Recombinant humanized anti-VEGF monoclonal antibody, intravitreal injection)) Dose:1.25mg(0.05 mL, Strength: 5 mg/0.2 mL/vial
Control drug	Lucentis® (Ranibizumab, intravitreal injection) Dose:0.5 mg(0.05mL), Strength: 2mg/0.2ml/vial
Study Leading Center	Peking Union Medical College Hospital
Principal Investigator	Professor You-Xin Chen
Study Centers:	Approximately 50-70 centers
Phase	III
Objectives	Primary Objectives: To compare the efficacy of TAB014 to Ranibizumab injection (Lucentis®) in patients with neovascular age-related macular degeneration. Secondary Objectives: • To compare the safety of TAB014 compared to Ranibizumab injection (Lucentis®) in patients with neovascular age-related macular degeneration • To evaluate the immunogenicity of TAB014 in neovascular age-related macular degeneration patients.
Study Design	This study is a randomized, multi-center, double blind, Lucenti® controlled non-inferiority study in neovascular age-related macular degeneration patients. The objective of this study is to compare the efficacy, safety of TAB014 and ranibizumab. It is planned to enroll a total of 488 subjects, 1:1 randomization, with 244 subjects in the TAB014 group, and 244 subjects in the Lucentis® group. The random stratification factor will be the PCV of the study eyes (determined as yes or no by the IRC); the BCVA of the study eye at baseline (< 24 letters or ⩾24 letters). This study consists of a screening period, randomization/baseline/first treatment, treatment period, and Final visit. The screening period is 28 days. After the subjects pass the screening, they will be randomly selected and the first dose will be given on the day of randomization. Then they will enter the treatment period, with intravitreal injection once every 4 weeks. The final visit will be conducted 4 weeks after the last treatment. The experimental group will receive TAB014 intravitreal injection once every 4 weeks, each dose to be 1.25mg(0.05mL); the control group to receive ranibizumab (Lucentis®) intravitreal injection

	once every 4 weeks at 0.5mg(0.05mL) per dose. The final visit is planned to be conducted in the week 52. BCVA (Best corrected visual acuity) will be evaluated by masked evaluators every 4 weeks. Subjects, investigators responsible for patient care, vision examiner (including BCVA assessors), research nurses, independent central reading center staff, and the sponsor are blinded. Unmasked pharmacist, unmasked nurse, unmasked treatment administration physician and unmasked research associates will take part in this study.

Inclusion Criteria& Exclusion Criteria	**Inclusion Criteria** (Patients need to fulfil all inclusion criteria): 1. Patients must be > 50 years old, male or female; 2. Independent central reading center confirmed active subfoveal or juxtafoveal choroidal neovascularization (CNV) secondary to neovascular age-related macular degeneration in the study eye (Active is defined as the presence of evidence of subretinal/intraretinal fluid, subretinal hyperreflective material, or leakage); 3. BCVA letter score between 18 and 73 (inclusive) by the ETDRS chart during the screening period and basseline; 4. In the study eye is confirmed by Independent central reading center: a) Total lesion area is ≤ 12 optic disc areas(30mm^2), b) Fibrosis, scarring or atrophy< 50% of total lesion area, and not involve the fovea centralis, c) Subretinal hemorrhage involving the fovea centralis, Intraretinal hemorrhage < 4 optic disc areas; 5. Able to understand and personally sign informed consent form. **Exclusion Criteria (**Patients who meet any of the following exclusion criteria will be excluded from participating in this study): 1. Ophthalmic Treatment history: a) Intravitreal injection of an anti-VEGF drug (ranibizumab, bevacizumab, aflibercept or conbercept, etc.) in any one eyes, anti-VEGF injection in the past 90 days in the non-study eye; and expect the study eye will not be able to discontinue the anti-neovascular treatment not in this study during the study period, or expect the non-study eye will need anti-neovascular treatment within 30 days after randomization; b) Prior vitrectomy, panretinal photocoagulation, ocular treatment or laser treatment for the fovea centralis/surgery for nAMD in the study eye; history of corneal transplantation or corneal dystrophy, treatment with verteporfin, external radiation therapy for head or eyes, transpupillary hypertherapy, expected that the above-mentioned treatment will be required during the research period; c) Prior intra-ocular (including cataract) surgery in the study eye within 90 days of randomization, or surgery to the exterior eye within 28 days of randomization, or expect intraocular surgery (including anterior segment surgery and posterior segment surgery) will be required during the study period; d) Prior intravitreal injection or implantation of corticosteroids/sustained-release corticosteroid preparations in the study eye in the past 180days before randomization; or prior other ocular corticosteroid injections except intravitreal injection in the past 30 days before randomization; or expect Intravitreal/periorbital corticosteroid injection by to(excluding topical preparations) in study period; e) PDT (Photodynamic Therapy) in the non-study eye within the past 30 days before screening, 2. SConfirmed to have a BCVA on ETDRS chart of < 18 letters during screening in non-stydy eye during the screen period of baseline; 3. Myopia more than -8.0 diopters of refractive error in study eye. For patients who have undergone refractive surgery or cataract surgery, refraction must not have been greater than -8.0 diopters prior to

surgery;

4. In study eye : a)absence of the crystalline lens (unless there has been artificial lens replacement), b) posterior capsule rupture or coloboma;c) Prior i YAG laser posterior capsulotomy within 30 days of randomization
5. As judged by the investigators, the study eye currently has a) affecting centre vision, or b) increase the safety risk to the patient, or c) affect the efficacy and safety evalucation or collection, d) not cause of nAMD eye diseases surgical or medical intervention
6. According to the judgment of the independent reading center, the study eye is currently complicated with: a) Central serous chorioretinopathy, or b) Vitreous hemorrhage, or c. CNV not caused by nAMD, or d) Retinal pigment epithelium tear, macular hole, macular telangiectasia and other macular abnormalities involving the macula, except for neovascular age-related macular degeneration, or e) Non-namd diseases that affect central vision;
7. During the screening period, the study eye had: a) uncontrolled glaucoma (e.g. intraocular pressure > 24 mmHg, after treatment with anti-glaucoma drugs), or b) Accepted external drainage surgery for glaucoma, or c) Late-stage glaucoma or optic neuropathy that affects or endangers the central visual field of the study eye;
8. At the time of randomization, any active intraocular, extraocular, or periorbital inflammation or infection (such as conjunctivitis, keratitis, scleritis, or endophthalmitis) in either eye;
9. A history of idiopathic or autoimmune-related uveitis in either eyeActive intraocular, extraocular, or periocular inflammation or infection in either eye at randomization (e.g. Conjunctivitis, keratitis, uveitis, or endophthalmitis);

Systemic condition

10. The detection of hepatitis B surface antigen (HBsAg) is positive, and the titer of hepatitis B virus deoxyribonucleic acid (HBV DNA) in peripheral blood is $\geqslant 1 \times 10^3$ IU/mL. If HBsAg is positive and the titer of HBV DNA in peripheral blood is detected, 1×10^3 IU/mL. If the researcher believes that the chronic hepatitis B of the subject is in a stable stage and does not increase the risk of the subject, the subject is eligible for inclusion. Positive for hepatitis C virus (HCV) antibody, positive for nucleic acid RNA, positive for Treponema pallidum antibody, and positive for human immunodeficiency virus (HIV) antibody
11. Poorly controlled hypertension in spite of appropriate therapy, a single systolic pressure measurement of >160mmHg, or 2 consecutive measurements with diastolic pressure >100mmHg;
12. Diabetic subjects with glycated hemoglobin >10%
13. At the time of randomization, the presence of any uncontrolled clinical conditions (e.g., severe psychiatric, neurological, metabolic, immunological, cardiovascular, respiratory, and other systemic diseases, as well as malignant tumors). Individuals with abnormal liver or kidney function (ALT, AST $\geqslant$ 2.5 times the upper limit of the normal range(ULN)). Individuals with total bilirubin $\geqslant$ 1.5 times ULN; creatinine (Crea), urea, or blood urea nitrogen (BUN) $\geqslant$ 1.2 times ULN; or coagulation function abnormalities

(prothrombin time > 3 seconds above ULN or activated partial thromboplastin time > 10 seconds above ULN). Those who have experienced any of the following cardiovascular events within 180 days prior to randomization, and which, in the investigator's judgment, may affect patient safety assessment or increase subject risk: myocardial infarction, unstable angina, history of coronary revascularization, history of cerebrovascular accident (including TIA), history of other thromboembolic diseases (such as thromboangiitis obliterans, pulmonary embolism, portal vein thrombosis, etc.), New York Heart Association (NYHA) Class ⩾ II heart failure, or severe unstable ventricular arrhythmias.

14. Prior significant allergic reactions to biological products, or known allergic reactions to bevacizumab, ranibizumab, or study related medication (including fluorescein or indocyanin green), pupillary dilating agents, anesthetic used by the patient during the study period, or anti-infective agents;
15. Systemic anti-VEGF therapy within 90 days prior to randomization is not permitted. However, the use of dietary supplements, vitamins, or minerals is allowed.
16. Randomized within 90 days of continuous systemic corticosteroid use for ⩾30 days, or systemic corticosteroid use within 5 days prior to randomization; or anticipated need for systemic corticosteroid use during the study period (intranasal, inhaled, topical skin, intra-articular, perianal corticosteroids, and short-term (continuous use <2 weeks) oral corticosteroids are permitted).
17. Necessity to continue use of prohibited agents (drugs known to be toxic to the lens, retina, or optic nerve, including deoxyamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, ethambutol);
18. Participate in any clinical trial involving drug or device treatment (except vitamins and minerals) within 90 days prior to randomization, and prohibit the use of any other investigational drugs or investigational interventions not in this study during the study period (for example, isovolumic blood dilution, vitreous tissue plasminogen activator);
19. Pregnant or breastfeeding women, or subjects (both male and female) who plan to become pregnant or father a child during the study period or within 6 months after study completion. Female patients with fertility who tested positive in pregnancy tests during the screening period or were unwilling to use reliable contraceptive methods during the study period, including: Hormonal methods for oral, implanted, injectable, or transdermal; Barrier methods with spermicide (diaphragm or condom + spermicide); Intrauterine device (IUD); Surgical sterilization of the male partner;
20. Other conditions that are considered not acceptable by the investigator.)

Study Endpoints	**Efficacy Assessment:** **<u>The primary efficacy indicator:</u>** Evaluate the change in BCVA of the study eye from baseline to week 52. **<u>The Secondary efficacy indicators:</u>** 1. To evaluate the change in BCVA of the study eye from baseline up to week 12, week 24 and week 36. 2. To evaluate the proportion of subjects with an increase in BCVA of >5, >10, and >15 letters in the study eye from baseline up to week 12, week 24 and 52. 3. To evaluate the proportion of subjects with a BCVA loss of <5, <10, < 15 letters in the study eye from baseline up to week 12, week 24 and 52. 4. Changes in central subfield thickness (CST) of the study eye at weeks 12, 24, 36, and 52, assessed by spectral-domain optical coherence tomography (SD-OCT) via an independent reading center, compared with baseline, between the two groups. 5. Change in CNV area size on fluorescein angiography (FA) of study eye as assessed by independent central reading center at week 24 and 52, compared to baseline. **<u>Safety assessment indicators:</u>** • Vital signs; • Physical examination; • Electrocardiogram (ECG); • Laboratory tests; • Ophthalmic examination; • Ocular and non-ocular adverse events and serious adverse events; • Adverse events of special concern (AESI) etc., Adverse events are encoded inaccordance with MedDRA terminology (version25.0 or above). According to **Appendix 3: Ocular Adverse Event Classification Table** and the NIA Guidelines for Adverse Events and Serious Adverse Events (September 2018 Edition), ocular and non-ocular adverse events, serious adverse events, adverse events of special concern (AESI), etc. were classified respectively. At the same time, correlation judgment and drug correlation judgment were conducted to evaluate the safety of the experimental group and the control group. Adverse events of special interest (AESI): Infectious endophthalmitis, non-infectious endophthalmitis (e.g. Iritis, vitreous inflammation and iridocyclitis), and elevated intraocular pressure (newly developed AE with intraocular pressure >24 mmHg and no response to treatment, except for transient elevation of intraocular pressure within 1 hour after injection of the study drug; Any adverse events (AE) with intraocular pressure ⩾35 mmHg and requiring treatment, retinal detachment/tear, retinal artery occlusion, iatrogenic traumatic cataract, and retinal pigment epithelial detachment that occur at any time; Systemic AESI: Thromboembolic events (e.g. venous thromboembolism, arterial

	thromboembolism) **Immunogenicity evaluation** Approximately 80 subjects with nAMD in one eye who had not received anti-VEGF treatment in both eyes or the contralateral eye throughout the study period were planned to undergo immunogenic blood collection before administration at weeks 0, 12, and 24, as well as at the final visit. The baseline and treatment period blood collection points were within 2 hours before each administration, and the final visit blood collection point was 28 (±7) days after the last administration. The immunogenicity of TAB014 will be evaluated by anti-drug antibodies and/or neutralizing antibodies.
Statistical Methods	**Sample Size:** Assuming the standard deviation for BCVA improvement after one year of ranibizumab (Lucentis®) therapy to be 14.0, the standard deviation under similar conditions for bevacizumab will be 15.0, taking a non-inferiority margin of -4.5, one sided level of significance to be 0.025, at 90% power, considering a 10% drop out rate, at 1:1 randomization, there should be 244 subjects in the TAB014 group, and 244 subjects in the ranibizumab group, totally 488 subjects. **Populations:** Randomized population set (RAND): Includes all subjects randomized. RAND is used to describe subject demographics and baseline characteristics. The RAND-based analysis will categorize subjects according to their randomized treatment groups. Full analysis set (FAS): Includes all subjects who have been randomized and used the investigational product at least one dose. Subjects will be analyzed according to their randomized treatment groups. Per protocol set (PPS): Includes all subjects in the FAS who have completed the first 3 doses within the first 3 months, received ⩾9 doses during the study, completed the primary efficacy endpoint assessment as specified in the protocol at Week 52, and have no major protocol deviations affecting the primary efficacy endpoint. The FAS set and PPS set will be used for statistical analysis of the primary efficacy endpoints. Since this is a non-inferiority study, the FAS set and the PPS set will be of equal importance. If the analysis results are inconsistent, the reasons for the inconsistency should be analyzed and reasonably explained. Safety Analysis Set (SS): All subjects who have received at least one dose of either study drug and have a documented post-baseline safety assessment. The SS set will be used for safety analysis, and subjects will be analyzed according to the actual treatment group received. Immunogenicity analysis set: Includes subjects who received at least one dose of either study drug and at least one post-baseline immunogenicity assessment. **Efficacy Analysis:** Primary efficacy endpoint:

	Changes in BCVA at 52 weeks compared to baseline will be analyzed using the analysis of covariance model (ANCOVA), in which the BCVA change compared to baseline will be studied as a dependent variable, the treatment group allocation and stratification factor (PCV or not) will be the independent variable, and baseline BCVA will be the covariate. Secondary efficacy endpoints: The continuous secondary efficacy endpoints will be analyzed using the same method as the primary efficacy endpoints: using ANCOVA and MMRM models to analyze separately, report the least squares mean, standard error of each treatment group relative to the change from baseline, and the difference between the two groups (TAB014-Lucentis®), standard error, 95% two-sided CI and corresponding P value. For categorical secondary efficacy endpoints, the number and proportion of subjects in each category according to each group will be reported together with the corresponding two-sided 95% exact CI (based on the Clopper-Person method), The difference in the proportion of subjects between the two groups after adjusting for stratification factor (PCV or not) and the 95% CI of the difference will be estimated using Mantel-Haenszel (MH) test. The Cochran-Mantel-Haenszel (CMH) method was used to compare the difference in the proportion of treated subjects after adjusting for the effect of stratification factor (PCV or not), and the P value of the comparison was reported. **Safety analysis:** Adverse events, serious adverse events, adverse events of special concern (AESI), laboratory tests (such as hematology, blood biochemistry, urine analysis), electrocardiogram, vital signs and physical examination will be used to assess safety. Group description analysis is conducted on all security data in the security analysis set. **Immunogenicity analysis:** Immunogenicity blood sampling will be performed in approximately 80 subjects with nAMD in one eye and no prior anti-VEGF therapy in the non-study eye in both groups. The number and percentage of TAB014 ADA/Nab-positive subjects at any evaluation time point (including baseline, any post-baseline visits, all planned visits, etc.) will be summarized and reported. Blood samples for ADA/NAb testing were collected at pre-dose on week 0, 12, and 24, as well as at the final visit (28 ± 7 days post-last dose). The incidence of treatment-emergent ADA/Nab positivity (and sample-level positivity rates) was summarized by actual treatment (TAB014 or ranibizumab(Lucentis®)).

1.2 ASSESSMENT SCHEDULE

Table 1-1 Study Flow Chart

Term	**Screening Period**	**Baseline/Randomization**	**Treatment period**												**Final visit[19]**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Week	-	W0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52
Dosing times		1	2	3	4	5	6	7	8	9	10	11	12	13	
Visit Window (Days)			+ 7	+ 7	+ 7	+ 7	+ 7	+ 7	+ 7	+ 7	+ 7	+ 7	+ 7	+ 7	+ 7
Informed Consent	V														
Demography / Medical History [1]	V														
Inclusion/Exclusion	V														
Height/weight[2]	V														
Physical Examination[2]	V	V			V			V			V				V
Vital Signs[2]	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Laboratory	V	V			V			V			V				V
Glycated hemoglobin detection [4]	V														
Blood pregnancy test 4	V														V
12 - lead ECG [5]	V	V			V			V			V				V
Chest radiography [6]	V														V
Infectious disease examination[7]	V														
BCVA[9]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
IOP measurement[10]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Slit lamp inspection[11]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU

Fundus examination[12]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
OCT[13]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
CF+ICGA+FFA[14]	OU	OU			OU			OU							OU
Randomization[15]		V													
TAB014/Ranibizumab[15]		SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	
Post-Injection evaluation[16]		OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	
Adverse events[17]		V	V	V	V	V	V	V	V	V	V	V	V	V	V
Concomitant Medication/therapy	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Immunogenicity Testing[18]		V			V			V							V

When evaluation is required, use 'V' to indicate it; 'OU' means both eyes need to be evaluated, and 'SE' means only the study eye requires evaluation.

1. Demographic data includes date of birth, age, gender, ethnicity, race, etc., record medical history of systemic within 6 months prior to the screening period; record any serious, unstable or uncontrolled systemic diseases; record any history of systemic diseases that may affect the validity and safety results of the study record the history of eye diseases within 2 years prior to the screening period; record any history of ophthalmology diseases that may affect the efficacy and safety results of the study; record the previous drug history within the 6 months prior to the screening period; record the history of systemic surgery and non-pharmaceutical treatment within 6 months before the screening period; record any history of eye surgeries and non-pharmaceutical treatments; record any history of anti-VEGF eye surgery; record any history of allergies; record the history of smoking and drinking.
2. Measure height and weight, and accep.t the results within 28 days before randomization. Vital signs include temperature, blood pressure, pulse, respiratory rate. The results of the perform physical examination and measure vital signs should be within 28 days before randomization. Vital signs should be checked before injection (within 24 hours) and 60 (± 30) minutes after injection, and physical examination should accept the results of 7 days before randomization.
3. Laboratory examination: The laboratory examination include: blood routine examination, Blood biochemistry, coagulation function， routine urine examination. Blood routine examination includes: red blood, white blood and platelet count and neutrophil, lymphocyte, eosinophil and basophil count and hemoglobin. Blood biochemistry includes sodium, potassium, chloride, bicarbonate, glucose, BUN urea/BUN, creatinine, calcium, phosphorus, magnesium, total bilirubin and direct bilirubin, total protein, albumin, ALT, AST, LDH, ALP and uric acid. The coagulate hemoglobin on function includes prothrombin time, INR and APTT. Urine routine includes urine glucose, urine protein, and pH. Laboratory tests during the screening and baseline periods may use results obtained within 14 days prior to randomization; for all other visits, laboratory tests must be performed within 7 days prior to dosing.
4. The test item for Glycated hemoglobin detection is haemoglobin A1c (HbA1c), the result of the examination in screening period should be within 28days before the randomization.
5. Suitable for women of childbearing age (The following conditions exempt the subject from the requirement of a blood pregnancy test: the subject has

undergone sterilization procedures such as hysterectomy and/or bilateral oophorectomy, and has had no menstrual period for 12 consecutive months (and is determined to be postmenopausal based on age and other relevant factors). However, subjects who have undergone bilateral tubal ligation are still required to undergo a blood pregnancy test.). A blood pregnancy test should be performed within 28 days before randomization). A blood pregnancy test result obtained within 28 days prior to randomization during the screening period is required, and an additional blood pregnancy test should also be conducted at the final visit. During the study period, the investigator may, at their discretion, decide whether additional pregnancy tests are necessary.

6. 12-lead ECG examination during screening should and baseline be performed within 14 days before randomization and baseline, for all other visits, ECG examintation must be performed within 7 days prior to dosing.
7. Chest X-ray examination includes anteroposterior and lateral examinations, examination during screening and baseline should be performed within 14 days before randomization (CT results can be accepted to replace chest X-ray results).
8. Virological screening: The blood HBsAg, HCV, HIV and syphilis test data within 3 months before randomization can be used. Subjects with positive hepatitis B surface antigen need to undergo HBV-DNA titer or quantitative test; those with hepatitis C virus (HCV) antibody positive need to undergo HCV-RNA test at the same time.
9. According to the ETDRS chart, the evaluation of BCVA should be performed within 14 days before randomization during the screening period, BCVA should be performed within 3 days during baseline. During the treatment period BCVA should be performed within 3 days before each dose.
10. IOP measurement: IOP will be measured using a tonometer (Non-contact tonometer) for both eyes at each visit, IOP measurement should be performed within 14 days before randomization during screening and baseline period, During the treatment period IOP measurement should be performed within 3 days before each dose.
11. Slit lamp examination will be measured for both eyes at each visit, accept within 14 days before randomization, during screening and baseline period, other treatment visits should be performed within 3 day before the dose.
12. Fundus examination will be measured for both eyes before treatment. During screening and baseline period, fundus examination should be measured within 14 days before randomization. Fundus examination should be measured within 3 days before treatment at each visit.
13. The OCT examination during the screening and baseline period accepts the examination results within 14 days before randomization, and the examinations of subsequent treatment visits should be within e day before the administration. Examination should be performed in both eyes, and the result keep two decimal places.
14. The CF（Color Fundus）, ICGA and FFA examination will be performed at screening, baseline, week 12, 24 and final visit, and the result keep two decimal places. The results of screening and baseline inspections within 14 days before randomization are accepted, and the results within 28 (±7) days after administration in the 8th week can be used in the week 12, and the results within 28 (±7) days after administration in the 20th week can be used in the week 24.
15. The randomization / baseline is defined as Day 1. The first dose must be performed at the Day 1, other treatment visits have ±7 day time window.
16. Assessment after inject: Measure the intraocular pressure of both eyes after each administration of TAB014/ ranibizumab (Noxide ®) within 60 (±10) minutes after injection.After the injection, check whether the subject's research eye can count fingers or see the movement of fingers clearly (within 15 minutes after the injection and administration, conduct digital inspection at 1 meter. If the subject cannot count fingers correctly at 1 meter, conduct

inspection at 2/3 meters. If the subject still cannot count fingers correctly, conduct inspection at 1/3 meters, and record the distance of digital vision. If the subject still cannot count fingers at 1/3 meters, conduct manual inspection at 2/3 meters, if it still cannot be manually, conduct manual inspection at 1/3 meters. If the subject does not have manual vision, conduct light perception inspection), to ensure that the central retinal artery has blood perfusion, and records. If there is no safety problem 60 minutes after each treatment, the subject can leave.

17. All AEs should be reported in accordance with Section 8.1 Adverse Events.
18. Blood samples for ADA/Nab are collected at week 0, 12, 24(pre-dose), and the final visit. For baseline and treatment period samples collected within 2 hours before each dose administration, for the final visit sample collected 28 (±7) days after the last dose administration, and 5mL of venous blood each time.
19. The final visit is conducted 28(±7) days after 13th dose. All assessments during the final visit are also required to be performed within 28 (±7) days after the 13th administration. Subjects who discontinued early were assessed according to the final visit procedures.

Note: All ocular examinations in this study were performed in both eyes. For OCT, intraocular pressure (IOP), color fundus photography (CF), indocyanine green angiography (ICGA), and fluorescein angiography (FFA), it is recommended that the same examination device be used for the same subject throughout the study.

2 BACKGROUND

Age-related macular degeneration (AMD) is a common cause of blindness, predominantly affecting the geriatric population. The projected number of people with age-related macular degeneration across the globe in the year 2020 will be 196 million (range: 140–261 million), with projection to rise to 288 million (range: 205–399 million) in 2040, and the largest number of cases will be found in Asia, with 113 million cases (range: 60–203 million) estimated for 2040; Europe is expected to be second to Asia with 69 million cases projected (range: 40-109 million), followed by Africa at 39 million (range:12–93 million), Latin America and the Caribbean come in at 39 million (range: 15–82million), North America at 25 million (range: 15–38million), and Oceania 2 million[1].

Although the pathogenesis of AMD development has not been completely elucidated, its development has been linked to an imbalance between local angiogenesis inducers and inhibitors caused by changes emanating from aging, oxidation, inflammation, compounded by changes in the Bruch's membrane over time. Associated factors for AMD development are age, sunlight exposure, vitamin deficiencies, excessive alcohol intake, smoking, and hyperlipidemia. Genetic polymorphisms may also have significance in its development[2]. A systematic review spanning 18 prospective cross-sectional studies and 6 case control studies, involving 113,780 persons with 17,236 cases of late AMD, linked to at least one of 16 pre-selected risk factors: smoking, previous cataract surgery, and a family history of AMD are consistent AMD associated risk factors, whereas risk factors with weaker and inconsistent associations are gender, ethnicity, diabetes, iris color, history of cerebrovascular disease, total and HDL cholesterol, and triglyceride levels, etc.[3].

AMD consists of dry and wet (neovascular) types. In the dry (non-exudative) type, cellular debris called drusen accumulates between the retina and the choroid, with resultant retinal atrophy and scarring. In the neovascular (exudative) type, which is more severe, blood vessels emanate from the choroid behind the retina, leaking exudate and fluid, and can potentially hemorrhage. Although the incidence of nAMD is significantly lower than that of dry AMD, 90% of nAMD patients have vision impairment of varying severity, and as a result of its rapid progression, it could lead to detrimental visual consequences. In addition, 50% of nAMD patients develop nAMD in the other eye within 5 years.

High expression of Vascular endothelial growth factor (VEGF) promotes the formation of CNV in the macular region, which is the leading cause of vision impairment in patients with AMD. VEGF is a member of the family of platelet-derived growth factors, and is highly specific for vascular formation and permeability induction in vascular endothelial cells. VEGF promotes angiogenesis, formation of new blood vessels, and microvascular permeability, causing blood vessel leakage. Drugs have been developed to target VEGF, to reverse AMD development, these include pegaptanib (Macugen, approved by US FDA in 2004), an anti-VEGF humanized monoclonal antibody bevacizumab (off label use, never approved). since 2005, followed by drugs that target the same pathway such as ranibizumab (2006/6 US FDA approved), aflibercept (2011/11 US FDA approved), conbercept (2014/4 CFDA approved), and brolucizumab (2019/10 US FDA approved).

In patients with age-related macular degeneration, there has been consistent, high-level evidence from 9 randomized controlled trials (RCTs) detecting no difference between bevacizumab and ranibizumab in mean BCVA improvement at 12 months. Similarly, there was moderate-strength evidence of no difference between bevacizumab and ranibizumab in the proportion of patients gaining 15 or more letters at 12 months. In comparing aflibercept to ranibizumab, two trials provided low-strength evidence of no difference between the drugs in the proportion of patients gaining 15 or more letters; however, the strength of evidence for a change in BCVA mean was insufficient due to inconsistent results in the two studies. Trials reported low rates of serious ocular adverse events in AMD patients and no differences were reported between drugs (moderate-

strength evidence). Systemic adverse events occurred slightly more often in these trials, but incidences were also similar between groups (moderate-strength evidence for intravitreal bevacizumab compared to ranibizumab; low-strength evidence for intravitreal aflibercept compared to ranibizumab). No studies compared the effectiveness or adverse impact of aflibercept to bevacizumab in this population[4].

Light iris patients make up the majority of patients enrolled in the previous phase 3 AMD trials. In the CATT and IVAN studies[5][6], disparities between ranibizumab and bevacizumab efficacy were not observed based on eye color. A subgroup analysis of Asian patients from VIEW 1 and VIEW 2 studies compared functional and morphologic outcomes at week 96 between intravitreal aflibercept 2 mg monthly (2q4) or 2mg bimonthly after 3 initial monthly doses (2q8) versus ranibizumab 0.5 mg monthly among Asian patients (n = 269) and white patients (n = 2044); no significant differences between intravitreal aflibercept and ranibizumab in mean gain in best-corrected visual acuity (10.23 and 8.35 vs. 8.51 letters), although reduction in central retinal thickness was greater for intravitreal aflibercept 2q4 (150.43 mm, P = 0.0075) and 2q8 (148.15 mm, P = 0.0126) than ranibizumab (119.46 mm)[7].

Ranibizumab (Lucentis®) has been approved by the China NMPA in the indication of nAMD. Bevacizumab has been used off label for the same indications since 2005, but has never received marketing approval.

Bevacizumab has comparable efficacy and safety to other anti-VEGF drugs in the management of nAMD patients confirmed through multiple randomized clinical trials[3][4][5][8]. However, ophthalmic off-label use has incurred infection concerns resulting from inadequately formulated drug product. TAB014 has been specifically designed for intravitreal administration。

TAB014 received IND number 2017L04523 on July 28th, 2017 from the China NMPA to initiate a phase I study in previously treated nAMD patients. Preliminary data demonstrated TAB014 to be safe and well tolerated. The phase III study is designed to demonstrate that TAB014 is non-inferior to ranibizumab for the treatment of nAMD. At the same time, BIODLINK also hopes to launch a high-quality drug with appropriate packaging and easy cavity injection, and also has price advantages.

2.1 STUDY DRUG OVERVIEW

TAB014 is a recombinant humanized anti-VEGF monoclonal antibody developed through genetic engineering by BIODLINK. TAB014 binds VEGF to prevent it from attaching to VEGF receptors, thus blocking downstream biological activity and prevents neovascularization [8]. In the retina, nAMD can be effectively controlled through inhibition of choroidal neovascularization. Invitro studies have shown that TAB014 is very powerful in the inhibition of HUVEC proliferation, migration, and new vessel formation. In vivo studies have shown TAB014 to be equally effective to ranibizumab in the control of neovascularization secondary to laser photocoagulation damage of the retina in Cynomolgus monkeys. The inhibitory effect showed a time-effect and dose-effect relationship during the observation period. TAB014 Monoclonal Antibody Injection has similar pharmacological effects to Bevacizumab and Ranibizumab (Lucentis®).

BIODLINK derived two drug products from its anti-VEGF drug substance, intravenous injection of TAB008 is for treating tumors such as colorectal cancer and lung cancer, and intravitreal injection of TAB014 is used to treat ophthalmic diseases such as nAMD.

2.2 NONCLINICAL STUDIES

Since both TAB014 Monoclonal Antibody Injection (hereinafter referred to as"TAB014") and TAB008 Monoclonal Antibody Injection (hereinafter referred to as"TAB008") are split and composed of anti-VEGF single antigen solution and are the same active ingredient, the study results of TAB008 were used in the in vitro study of TAB014.

2.2.1 Pharmacokinetics study

The pharmacokinetic study of different doses of intravitreal injection of TAB014 in both eyes of healthy cynomolgus monkeys was carried out and compared with intravitreal injection of bevacizumab. The results showed that there was no significant difference in serum kinetic parameters between male and female animals in TAB014 groups ($p > 0.05$). The peak drug concentration in serum, aqueous humor and vitreous fluid and serum drug exposure were positively correlated with the administered dose. The exposure of drugs in vitreous fluid was the highest. In the TAB014 low-dose group, the drug exposure in vitreous fluid was 25 and 28 times higher than that in serum, respectively. At the same dose (1.25 mg/eye), there was no significant difference in the pharmacokinetic parameters of the drug in serum, aqueous humor and vitreous fluid between TAB014 and the control (bevacizumab) after vitreous injection ($p > 0.05$).

The ocular tissue distribution characteristics of TAB014 in New Zealand rabbits were studied, and the ocular distribution of ^{125}I-TAB014 from high to low was: vitreous body, retina, cornea, aqueous humor, bulbar conjunctiva, plasma, and lower eyelid. The drug distribution in the target tissue (retina) is second only to the vitreous at the administration site and is significantly higher than that in other tissues. The AUC of the drug in plasma was approximately 0.88% of that in the vitreous (as precipitated radioactivity), suggesting relatively small systemic exposure. ^{125}I-TAB014 concentrations in the retina, cornea, aqueous humor, bulbar conjunctiva, and lower eyelid peaked at 24 hours after administration and at 3 days (72 hours) in the vitreous. There was basically no significant gender difference in metabolic characteristics between animals of different genders. The above results suggest that intravitreal administration can increase the drug concentration in target tissues, and then indicate that vitreous injection of TAB014 has a direct, rapid, efficient and moderate targeting effect.

2.2.2 Pharmacodynamics Study.

2.2.2.1 In vitro

The affinity of TAB008 for VEGF and Fc receptors is comparable to Avastin®. The binding activity of different batches of TAB008 for VEGF, Fc receptor and C1q complement was similar and consistent with Avastin®. TAB008 and Avastin® did not demonstrate antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytoxicity (CDC). TAB008 could significantly inhibit the activation of VEGFR2/KDR and its downstream signaling pathways in VEGF-stimulated HUVEC, and significantly inhibit the proliferation and migration of VEGF-stimulated HUVEC and the sprouting of rat arterial ring microvessels. Its mechanism of action was consistent with Avastin®, and its biological activity in vitro was comparable to Avastin®.

2.2.2.2 In vivo

A single vitreous injection of all treatment groups reduced the fluorescence leakage area when assessed by fluorescein angiography, and decreased the subretinal height of objects with high reflection signals on optical coherence tomography. The inhibitory effects of 1.25 mg/eye TAB014, 0.5 mg/eye ranibizumab and 1.25 mg/eye bevacizumb on CNV were comparable. The inhibitory effect of TAB014 was monitored during the 14-day observation period following administration, and was observed to be both time-dependent and dose-dependent. The above results demonstrate that TAB014 has a significant inhibitory effect on CNV.

2.2.2.3 Safety Pharmacology

A safety pharmacology study of TAB014 was performed concurrently with the 6 weeks repeat doses toxicity study, in order to evaluate the potential effects of TAB014 on the central nervous system, cardiovascular system and respiratory system.

TAB014 was administered to cynomolgus monkeys at doses of 1.25 and 2.5 mg/eye/time, once every two weeks for 4 injections. In combination with observation of toxicity indicators, monitoring of safety pharmacological indicators was performed. No marked abnormality was observed in mental status, behavioral activities, body temperature and respiration rate of animals

in either group. ECG examination at various time points did not reveal test article associated regular change in heart rate, P-R interval, QT interval, QRS duration, or other ECG parameters. No abnormal ECG waveform was observed. There was no significant effect on the central nervous system, cardiovascular system, or respiratory system of cynomolgus monkeys.

2.2.3 Toxicity

2.2.3.1 Single-dose Toxicity

In the toxicity test of TAB008 monoclonal antibody injection, no obvious abnormal reaction was observed in ICR mice, and no obvious donor-related gross and microscopic toxic pathological changes were observed. The maximum tolerated dose (MTD) was ≥ 625 mg/kg. In the intravenous toxicity test in cynomolgus monkeys, only AST indicators were transiently increased, and no other significant toxic reactions were observed. The maximum tolerated dose (MTD) was ≥ 400 mg/kg. The proposed clinical dose of 1.25 mg/eye of TAB014 was much lower than the MTD dose of TAB008 described above, so no toxicity test of intravitreal injection was conducted.

2.2.3.2 Repeat-dose Toxicity

In order to evaluate the potential toxicities of repeat use of TAB014 in support of a proposed clinical study, a 6-week IVT repeat dose study of TAB014, with a 4-week recovery period, was performed in cynomolgus monkeys. Clinical observation, body weight, body weight gain, body temperature, ECG parameters, blood cell count, coagulation function, blood biochemistry, urinalysis, organ weight, gross anatomy and histopathological examination showed no TAB014-related changes. Additionally, when a local irritation was performed, no abnormalities were observed in the eyelid, cornea, sclera, iris, pupil or lens during the experimental period. No anti-TAB014 antibodies were detected in all animals throughout the study.

Intravitreal injection of TAB014 can aggravate conjunctival congestion and cause grayish white punctate particles of consistent size in the anterior chamber and vitreous. At the end of the test, the punctate particles in the anterior chamber have been completely recovered, and punctate particles are still observed in the vitreous, but showing a tendency of recovery.

The peak serum drug concentration and serum drug exposure were positively correlated with the administered dose. The concentration of TAB014 in aqueous humor after last dose administered was about 4 times of the peak serum drug concentration after three doses, and the concentration of TAB014 in aqueous humor was positively correlated with the dose. Under the conditions of this test, the no-observed-adverse-effect level (NOAEL) of TAB014 was 2.5 mg/eye/dose, and the AUCinf after the 3rd dose was 11.08 h • mg/mL in male animals and 17.95 h • mg/mL in female animals.

2.2.3.3 Genetic Toxicity and Carcinogenicity Toxicity

In order to further evaluate the potential effect of TAB014 on the immune system of cynomolgus monkeys, the immunotoxicity and immunogenicity studies were performed concurrently with the repeat dose IVT injection study.

During the studies, there was no immune-related abnormal reaction in the vehicle control group, nor in TAB014 groups. There were no test article-related regularity changes in T-lymphocyte subsets, serum immunoglobulins, and cytokines (IL-2, IL-4, TNF-α and IFN-γ). No anti-drug antibody was detected in all animal serum samples. In terms of pathological examination, lymphoid organ / tissue gross anatomy did not show obvious abnormalities in thymus, spleen weight / coefficient and other indicators.

2.2.3.4 Tissue Cross Reactivity (TCR) Study

In addition, the specific bindings of TAB008 (10 μg/mL) and Avastin (10 μg/mL) with 31 kinds

of normal SD rat tissues, 31 kinds of normal cynomolgus monkey tissues and 31 kinds of normal human tissues were investigated. TAB008 and Avastin showed no cross reactivity with the tested normal tissues.

The tissue cross reactivity of TAB014 was compared to Avastin in 32 types of New Zealand rabbit tissues. Biotinylated TAB014 (5μg/mL and 10 μg/mL) and Avastin (10 μg/mL) showed no specific binding with normal New Zealand rabbit tissues.

2.2.3.5 Special Toxicity Study

- Hypersensitive Study

Active systemic anaphylaxis test in guinea pigs was carried out for TAB008; however, at the proposed clinical dose of TAB014 of 1.25 mg/eye, the amount of drug entering blood circulation was very small, and its exposure was much lower than the clinical dose of TAB008. Therefore, hypersensitive Study was not performed for TAB014.

In the low-dose TAB008 group, two animals showed allergic symptoms of different severity such as pilo-erection, scratching nose, sneezing, coughing, urination, defecation, ataxia, spasm, cheyne-stokes respiration and death. No animals in the high-dose TAB008 group showed allergic symptoms. Based on the results, TAB008(Sensitization doses 5, 25 mg/kg, challenge doses 10, 50 mg/kg) was positive in the systemic active anaphylaxis reaction study in guinea pigs.

- Hemolysis Test

TAB008 was evaluated in vitro at 1.4 and 16.5 mg/mL to determine its hemolysis or aggregation effect using a hemolysis test with RBCs. TAB008 injection had a hemolysis effect, but no aggregation effect, at 16.5 mg/mL, and had no hemolysis or aggregation effect at 1.4 mg/mL in hemolysis test using rabbit RBCs. The results were similar to the marketed comparator, Avastin.

The administration route of TAB014 was vitreous injection, and the proposed clinical dose was much lower than the clinical dose of TAB008, suggesting that TAB014 may not cause hemolysis in clinical practice.

- Local Irritation Test

TAB014 was evaluated for irritation to the localized tissues surrounding the injection site in order to characterize the safety profile prior to initiating clinical studies. Local irritation endpoints were assessed as part of the repeat dose toxicity study of TAB014 in cynomolgus monkeys. Briefly, no serious local irritation was induced by test article administration in eyelid, cornea, sclera, iris, pupil, and lens.

In summary, pharmacodynamics studies have shown that TAB014 has similar efficacy to anti-VEGF monoclonal antibodies such as ranibizumab; toxicity studies have shown that TAB014 is safe by vitreous injection.

More non-clinical details refer to TAB014 IB[9].

2.3 CLINICAL OVERVIEW

2.3.1 Clinical trial of TAB014

TAB014 is a recombinant humanized anti-VEGF monoclonal antibody developed by BIODLINK[10], which was approved by CFDA in July 2017 (Approval No.: 2017L04523). A phase I clinical study is currently ongoing.

The phase 1 dose escalation clinical trial in previously treated nAMD patients is presently ongoing. The aim of the study is to evaluate the safety, tolerability, and serum pharmacokinetics after intravitreous injection. The initial pilot phase enrolled 2 subjects who received multiple doses

(once every 28 days for a total of 3 administrations). Due to the limited sample size, the data proved insufficient to inform the blood sampling schedule design and dosing interval determination for the main trial. Subsequently, 3 additional subjects were enrolled in an updated pilot phase involving single-dose administration. These subjects were monitored for dose-limiting toxicity (DLT) through Day 42 post-dose. The safety profile of TAB014 monoclonal antibody injection was evaluated over the 42-day observation period. The main trial was subsequently designed with two dose groups, 1.25mg (0.05ml) and 2.5mg (0.1mL) dosages with 8 patients enrolled per dose level. After the first intravitreal injection, patients are followed for 28 days for observation of dose limiting toxicity, and if none reported, a further 2 doses will be given at 28 day intervals. As of July 2020, 1.25mgdose group and 2.50mg(0.10mL) dose group study have been completed, with a total of 16 nAMD patients enrolled[11].

The safety results of the TAB014 Phase I study formal trial showed that a total of 16 subjects were enrolled in the formal trial phase, including 8 subjects in the low-dose group (1.25mg) and 8 subjects in the high-dose group (2.50mg). The subjects were administered the drug on days 0, 28, and 56 (a total of 3 times). Among them, two subjects (with screening numbers S0302 and S0303, both in the 1.25 mg low-dose group) withdrew from the trial prematurely and only received two doses of the trial drug (on day 0 and day 28), while the remaining subjects were administered the drug as required by the protocol (three doses). All 16 subjects were included in the safety analysis set (SS). Based on the Safety Analysis Set (SS), during the trial period, 15 subjects (93.8%) reported a total of 45 AES, among which 12 subjects (75%) reported a total of 24 TEAEs. Only one subject in the high-dose group experienced one case of TEAE with a severity of ⩾ grade 3, which was hypertension and was not related to the study drug. 3 subjects (18.8%) experienced 5 cases of TEAE related to the study drug. No TEAE, SAE or DLTS that led to death, drug suspension or withdrawal from the trial occurred. The results of the formal Phase I trial of TAB014 indicate that the overall safety of the study drug TAB014 monoclonal antibody injection is relatively good.

The pharmacokinetic results of TAB014 phase I study showed that after a single intravitreal injection administration in the low-dose group and the high-dose group, the plasma drug concentration reached its peak approximately 6-7 days later, with C_{max} being 117.9±17.26 ng/mL and 181.9±52.24 ng/mL, respectively. The plasma exposure level increased with the increase of the administration dose ($AUC_{0\text{-}inf}$ in the low-dose group and the high-dose group was 4193±1098.45 ng·day/mL and 6475.1±2038.73 ng·day/mL, respectively; The plasma exposure level increased with the increase of the administration dose ($AUC_{0\text{-}inf}$ in the low-dose group and the high-dose group was 4193±1098.45 ng·day/mL and 6475.1±2038.73 ng·day/mL, respectively; The $AUC_{0\text{-}t}$ in the low-dose group and the high-dose group was 2414.6±218.55 ng·day/mL and 3722.3±1004.47 ng·day/mL respectively, the increase in exposure was lower than the increase in dose; $t_{1/2}$ were 19.7±7.93 days and 19.0±5.43 days respectively, and the CL/F were 315.1±78.55 mL/day and 414.8±117.88 mL/day respectively

After the third intravitreal injection administration in the low-dose group and the high-dose group, the plasma drug concentration reached the peak approximately 3-5 days, with C_{max} being 174.2±18.5 ng/mL and 303.4±85.87 ng/mL; the plasma exposure level increased with the increase of the administration dose ($AUC_{0\text{-}inf}$ in the low-dose group and the high-dose group was 5317.2±722.55 ng·day/mL and 8447.1±2958.78 ng·day/mL; The $AUC_{0\text{-}28\ days}$ of the low-dose group and the high-dose group were 2837.8±719.7 ng·day/mL and 7697.5±2406.69 ng·day/mL, respectively. The $t_{1/2}$ of the two groups was 17.9±5.29 days and 14.4±2.63 days respectively, and the CL/F was 363.4±17.06 mL/day and 452.7±109.29 mL/day respectively.

Compared with the pharmacokinetic parameters of the first administration of TAB014 monoclonal antibody injection, the C_{max} and AUC after the third administration in both the low-dose and high-dose groups were higher than those after the first administration. The AI (C_{max}) of the low-dose group and the high-dose group was 155.9±22.79% and 170.4±41.55% respectively, the AI (AUC) of the low-dose group and the high-dose group was 149±8.75% and 147.5±25.45%

respectively, and the average accumulation coefficient was between 125% and 200%. Both the low-dose group and the high-dose group showed mild accumulation.

The immunogenicity results of TAB014 Phase I study showed that based on the safety analysis set (SS), the results of the formal trial indicated that in the high-dose group, only one case (12.5%) of the subjects had their anti-TAB014 antibodies change from negative at baseline to positive after administration. The positive result occurred on the 112th day after administration (i.e., the 56th day after the third administration). All results in the low-dose group were negative.

The results of VEGF levels in TAB014 phase I study show that the results of the formal trial stage indicate that the average VEGF levels in both the low-dose group and the high-dose group almost all decreased at each time point after the first and third administrations. At baseline, the average plasma VEGF of the low-dose group and the high-dose group was 31.8±4.9 pg/mL and 53.5±23.36 pg/mL, respectively. The average value of the relative baseline change after the first administration of the two groups at each time point was [-0.2, -7.4] pg/mL and [-0.8, -19.5] pg/mL, respectively. The average values of the relative baseline changes at each time point after the third administration were [-0.4, -8.9] pg/mL and [-8.6, -23.5] pg/mL, respectively.

The efficacy results of TAB014 Phase I study showed that, based on the full analysis set (FAS), the research results of the formal trial indicated that after treatment with the study drug TAB014 monoclonal antibody injection, the best corrected visual acuity (BCVA) of both groups increased compared with the baseline. The thickness of the fovea centralis of the macula, the thickness of the fovea centralis subregion of the retina, the total area of CNV and the total area of CNV leakage in both groups decreased after treatment. Among them, the thickness of the fovea centralis of the macula and the thickness of the fovea centralis subregion of the retina showed a trend of greater decrease in the low-dose group than in the high-dose group 12 weeks after the first administration. The scores of the VFQ-25 scale in both groups increased after treatment.

Overall, the results of the TAB014 Phase I study indicated that the overall safety of the TAB014 monoclonal antibody injection was good and tolerable, and no DLT events occurred. The number of TEAE related to the study drug in the high-dose group was higher than that in the low-dose group. After intravitreal injection of TAB014 monoclonal antibody injection, it is absorbed in the eye and enters the systemic circulation. The peak is reached 6-7 days after intravitreal injection of TAB014 monoclonal antibody injection. The systemic exposure is relatively low. Cmax and AUC0-inf increase with the increase of dose after a single administration, and the mean t1/2 is 14.4-19.7 days. After multiple administrations, mild accumulation occurred in both dose groups. The efficacy of TAB014 monoclonal antibody injection in the treatment of wAMD was preliminarily explored. Both treatment groups showed improvements in efficacy indicators such as BCVA, CMT, and CSFT.

2.3.2 TAB008 clinical trial summary

TAB008 (TAB008 and TAB014 share the drug substance of TOT anti-VEGF monoclonal antibody in different strengths) is a bevacizumab biosimilar, and is to be used for the treatment of colorectal and non-small cell lung cancers, IND clinical trial approval granted by the China CDE in 2016 (2016L01456), a phase I bioequivalence study, and a phase III study in NSCLC have been completed.

TAB008 has been confirmed to be bio-equivalent in a randomized phase I study[12] compared to bevacizumab originator sourced from Europe. One hundred normal healthy male volunteers were randomized to TAB008 or Avastin groups, 1mg/kg dose was given over 90 min, and patients followed up for 99 days. The treatment group ratios of LS geometric means for the three primary PK parameters were fully contained within the bioequivalence limits of 80.00–125.00% (90% CI was 103.66–118.33% for C_{max}, 94.32–111.72% for AUC0-t, and 94.69–112.23% for AUC0-∞). Safety parameters were also comparable between the 2 groups, all TEAEs were mild or moderate,

with resolution on follow up. TEAEs were reported for 24 (49.0%) subjects in the TAB008 group and 22 (44.0%) subjects in the Avastin® group. TEAEs considered by the investigator to be related to the study drug were reported for 19 (38.8%) subjects in the TAB008 group and 19 (38.0%) subjects in the Avastin® group. NCI-CTCAE Grade 3 TEAEs were reported for one (2.0%) subject in the TAB008 group and three (6.0%) subjects in the Avastin® group. There were no Grade 4 or 5 TEAEs, SAEs, or deaths during the study, and no TEAEs leading to treatment discontinuation. Hypertriglyceridemia was the most frequently reported TEAE in both the TAB008 (10.2%) and Avastin® (8.0%) groups. Clinically significant increases in triglycerides, uric acid, and liver function test results (alanine aminotransferase total bilirubin, and direct bilirubin), as well as hypertension were observed in both groups. ECG and physical examination did not reveal any clinically relevant abnormalities in either group. One subject in each group tested positive for anti-drug antibodies and subsequently returned to ADA negative. TAB008 Monoclonal Antibody Injection was safe and well tolerated and demonstrated safety profiles comparable with those of Avastin®.

A phase III clinical study comparing TAB008 monoclonal antibody in combination with chemotherapy versus bevacizumab (Avastin®) in combination with chemotherapy, conducted among 549 patients with non-small cell lung cancer (NSCLC), also demonstrated similar efficacy and safety between the two groups. The steady-state trough concentrations of TAB008 and bevacizumab exhibited bioequivalence. BIODLINK has submitted the application for TAB008 as a biosimilar of bevacizumab(Avastin®), and has received marketing approval from the National Medical Products Administration (NMPA).

2.4 KNOWN AND POTENTIAL RISKS TO HUMAN SUBJECTS

2.4.1 Retrospective statistical analysis

Fung AE,[13] designed an internet-based survey to collect safety data from intravitreal bevacizumab (IVB) administration, from 70 centers located in 12 countries, with an accumulated 7113 injections prescribed to 5228 patients. Doctor-reported adverse events included corneal abrasion, lens injury, infectious endophthalmitis, retinal detachment, inflammation or uveitis, cataract progression, acute vision loss, central retinal artery occlusion, subretinal haemorrhage, retinal pigment epithelium tears, blood pressure elevation, transient ischaemic attack, cerebrovascular accident and death. No adverse event exceeded 0.21%. Self-reporting of adverse events after IVB did not pick up increased drug-related ocular or systemic events, suggesting IVB to be safe.

In a retrospective cohort study[14], 146,942 AMD patients were analyzed to examine the risks of all-cause mortality, incident myocardial infarction, bleeding, and incident stroke during recent AMD treatment. Neither bevacizumab nor ranibizumab was associated with increased risks of mortality, myocardial infarction, bleeding, or stroke compared with photodynamic therapy or pegaptanib use.

2.4.2 Infectious Endophthalmitis and Retinal Detachment

A total of 1,265 patients were injected with bevacizumab for diseases such as proliferative diabetic retinopathy, diabetic macular edema, retinal vein occlusions, and CNV resulting from several etiologies including AMD at eight Latin American institutions from 1 September 2005 to 31 January 2006 [14]. Ocular complications reported include 7 (0.16%) bacterial endophthalmitis, 7 (0.16%) tractional retinal detachments, 4 (0.09%) uveitis, and a case (0.02%) each of rhegmatogenous retinal detachment and vitreous hemorrhage. This study demonstrated that repeated intravitreal injections of either 1.25 mg or 2.5 mg of bevacizumab appears to be safe and well tolerated during the first year, and emphasizes the importance of aseptic techniques. In addition, patients should be monitored for early infection after injection.

2.4.3 Intraocular Pressure

A prospective study enrolled a total of 291 eyes with macular edema (ME) or active CNV, all were treated with a single 1.25 mg (0.05 mL) bevacizumab intravitreal injection[17]. Changes in intraocular pressure were measured over time using the non-study eye as control. Mean baseline IOP was 18.0±5.9 mmHg and 16.9±6.0 mmHg in the treated eye versus the non-study eye. Post injection IOP rose to 42.1±14.5 mmHg in the treated eye compared to 17.5±6.0 mmHg in the non-study eye.

The IOP variation was statistically significant in treated and control eyes (P<0.001 and P=0.003, respectively). Post injection IOPs higher than 50 mmHg were documented in 32.0% of the eyes. The IOP spike that occurs after the intravitreal injection of bevacizumab is usually transient, with IOP returning to a safer range (25-30 mmHg) within 15 to 30 minutes, without a paracentesis or glaucoma medications, in most patients. Subconjunctival reflux was present in 21.3% and correlated with a dampened IOP escalation (P<0.001).

Segal O et al. [17] reviewed consecutive cases of persistent IOP elevation after IVB injection for exudative AMD. A total of 424 patients (528 eyes) received 1796 intravitreal injections of bevacizumab. Persistent IOP elevation was documented in 19 eyes (3.6%, 19/528) of 18 patients (4.2%, 18/424), with IOP rise to 30-70 mmHg at 3-30 days after injection.

Kim D et al.[18] recorded IOP in 83 eyes of AMD patients who received intravitreal injections of bevacizumab. IOP measurements were analyzed at baseline, 6, 12, 18, and 24 months, and at the last follow-up after injection. There was no significant escalation in IOP compared to baseline IOP (14.11±2.76 mm Hg) after multiple intravitreal injections of bevacizumab (P>0.05). In the treatment group prescribed ≥4 injections, mean IOP measurements were not higher compared with the group which had <4 injections during the follow-up period (P>0.05).

Mathalone N et al.[19]observed IOP in 174 consecutive patients (201 eyes) after receiving IVB (1.25 mg/0.05 mL) as treatment for neovascular AMD. The results showed that persistent IOP increased with shorter intervals between injections. AMD eyes that receive IVB injections need to be monitored for IOP changes, especially those in which the intervals between injections are <8 weeks. Hollands H et al.[20] reported on IOP change in 104 AMD patients who received IVB. Elevated IOP 30 minutes after injection was observed in a significant percentage of patients, but the IOP of almost all patients' returned to a safe range (<25 mm Hg) within 30 minutes. There were individual patients with elevated IOP.

2.4.4 Hypertension

Ziemsen F et al.[21] looked for haemodynamic features of patients at higher risk of developing cardiovascular events after bevacizumab injection. Ambulatory blood pressure monitoring (AMBP) was performed in 14 hypertensive patients receiving 1.25 mg intraocular bevacizumab for either CNV or central retinal vein occlusion (CRVO). Abnormally high BP was found in the pre-injection measurement, even under anti-hypertensive treatment of the patients with CNV or CRVO. No general increase in BP was seen after the intravitreal injection (P = 0.01), although significantly reduced nocturnal dipping occurred as compared to before the injection (P = 0.006). A decline in serum VEGF-A was found to correspond to measureable levels of serum bevacizumab (up to 90 ng/mL). Although serum VEGF-A was decreased in individual patients, mean blood pressure, heart rate, and pulse pressure did not appear to be generally increased after bevacizumab administration. Hypertension, especially for patients with high risk of cardiovascular events, is a systemic adverse event which should be closely monitored.

2.4.5 Thrombotic Events

A meta-analysis[23]]of 8341 AMD patients undergoing vitreous body injection with ranibizumab, bevacizumab or aflibercept, documented serious adverse events (vascular death, any death, stroke, myocardial infarction, transient ischaemic attack) and thrombotic events, concluded that systemic thrombotic events occurred more often than placebo(Incidence of thrombotic events in bevacizumab 1.25 mg and ranibizumab 0.5mg group are respectively 4.12% and 3.94%).

2.4.6 Transient Ischemic Attack (TIA)

Research[23] has shown that the incidence rates of cerebrovascular accident (CVA) and TIA following anti-VEGF therapy (IVB and IVR injection) were lower than 0.07 per 100 injections. Many factors impacted the incidence of adverse reactions, such as age, past medical history and so on.

2.4.7 Gastrointestinal System

Gastrointestinal adverse reactions included nausea, gastrointestinal bleeding, gastrointestinal disorders, cardiac mucosal tear and so on. Among them, gastrointestinal bleeding is the most common non-ocular bleeding adverse reaction

3 STUDY OBJECTIVE AND ENDPOINTS

3.1 STUDY OBJECTIVE

In this study, we will compare the efficacy and safety of TAB014 to ranibizumab in patients with neovascular age-related macular degeneration to demonstrate that intravitreal injection of TAB014 (1.25 mg) every 4 weeks is non-inferior to the standard of care ranibizumab (0.5 mg) in patients with nAMD.

3.1.1 Primary objective

To compare the efficacy of TAB014 to ranibizumab in patients with nAMD.

3.1.2 Secondary objective

To compare the safety of TAB014 to ranibizumab in patients with nAMD.

To evaluate the immunogenicity of TAB014 in patients with nAMD.

3.2 STUDY ENDPOINTS

3.2.1 Primary efficacy indicator

To evaluate the change in BCVA of the study eye at week 52 compared to baseline.

3.2.2 Secondary efficacy indicators

1) To evaluate the change in BCVA of the study eye from baseline to week 12, 24 and 36.
2) To evaluate the proportion of patients with an increase in BCVA of >5, >10, and >15 letters in the study eye from baseline to week 12, 24 and 52.
3) To evaluate the proportion of patients with a BCVA loss of <5, <10, < 15 letters in the study eye from baseline to week 12, 24 and 52.
4) Changes in central subfield thickness (CST) of the study eye at weeks 12, 24, 36, and 52, assessed by spectral-domain optical coherence tomography (SD-OCT) via an independent reading center, compared with baseline, between the two groups.
5) Change in CNV area on fluorescein angiography as assessed by independent central reading center at weeks 12, 24 and 52, compared to baseline.

3.2.3 Safety evaluation

Safety examinations include vital signs, physical examination, electrocardiogram (ECG), laboratory tests, ophthalmic examination, ocular and non-ocular adverse events and serious adverse events, adverse events of special concern (AESI) etc., encoded in accordance with MedDRA terms (version25.0 or above). According to Appendix 3: Ocular Adverse Event Classification Table and the NIA Guidelines for Adverse Events and Serious Adverse Events

(September 2018 Edition), ocular and non-ocular adverse events, serious adverse events, adverse events of special concern (AESI), etc. were classified respectively. At the same time, correlation judgment and drug correlation judgment were conducted to evaluate the safety of the experimental group and the control group.

3.2.4 Immunogenicity evaluation

Approximately 80 subjects with nAMD in one eye who had not received anti-VEGF treatment in both eyes or the contralateral eye throughout the study period were planned to undergo immunogenic blood collection before administration at week 0, 12, 24 and the final visit. The immunogenicity of TAB014 will be evaluated by anti-drug antibodies and/or neutralizing antibodies.

4 STUDY PLAN

4.1 STUDY DESIGN

This study is a randomized, multi-center, double blind, Lucentis® controlled non-inferiority study in neovascular age-related macular degeneration patients. The objective of this study is to compare the efficacy, safety of TAB014 to Lucentis® in patients with neovascular age-related macular degeneration. It is planned to enroll a total of 488 subjects, with 244 subjects each in the TAB014 and Lucentis® groups. The random stratification factor was the PCV of the study eyes (determined as yes or no by the IRC); the BCVA of the study eye at baseline (< 24 letters or ⩾24 letters).

This study adopted a double-blind design, patients, investigators responsible for patient care, vision examiner (including BCVA assessors), study nurses, independent central reading center staffs, and the sponsor remained blind.

4.2 RATIONALE OF STUDY DESIGN

This Phase III study was designed and conducted in accordance with the "Guiding Principles for Non-Inferiority Design Clinical Trials"[27] and the "Technical Guiding Principles for Clinical Research of Therapeutic Drugs for Age-Related Macular Degeneration" [30] issued by the Center for Drug Evaluation of the National Medical Products Administration in September 2020.

Meta-analyses of multiple randomized clinical trials have confirmed that bevacizumab 1.25mg and ranibizumab (Lucentis®) 0.5mg used to treat nAMD, demonstrated no significant difference in terms of efficacy and safety [3][4][5]. In the TAB014 phase I clinical study[11], the dose of 1.25mg was safe and well tolerated, with observation of preliminary efficacy. And it shows a better therapeutic trend compared with the 2.5mg dose group. With Avastin 1.25mg monthly used to treat nAMD wildly in real world， TAB014 1.25mg will be recommend in phase 3 trial.

Ranibizumab (Lucentis®) was approved by the FDA in 2005 for the treatment of neovascular age-related macular degeneration, and is recommended by the American Academy of Ophthalmology[24] as standard of care for nAMD, followed by the National Medical Products Administration of China in 2012. According to the (Lucentis®) package insert[25], Lucentis® 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once 4 weeks. Therefore, ranibizumab (Lucentis®, 0.5mg intravitreally once 4 weeks) was chosen as the control drug.

Combined data analysis of 3 studies of ranibizumab compared to placebo[26] (ANCHOR study, MARINA study, PIER study), BCVA improved by 17.8 words on average after 1 year of ranibizumab (Lucentis®) treatment(95% CI 15.95, 19.65). According to the NMPA guidance “Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry”[27], it is assumed that the difference in efficacy between active control and placebo is represented by M1,

and the non-inferiority threshold M2 is usually set as (1-f) M1. Since the main evaluation index is a high-quality index, M1 is the lower limit of 95% CI, which is 15.95. The objective of this non-inferiority trial is to prove that TAB014 retains a significant part of the efficacy of ranibizumab (Lucentis®). And considering the variability of previous evidence and the constant assumptions, f is set to be a relatively conservative 70%, it means that the maximum acceptable non-inferiority level is (1-70%) M1, that is, 30% of 15.95=4.785. In addition, the minimal clinically significant improvement of BCVA in nAMD is an increase of at least 10 letters[28], improvement of more than 5 letters over is considered clinically significant improvement [33] in BCVA. Thus 4.5 letters are adopted as the non-inferiority threshold.

Regarding the therapeutic effect evaluation indicators and the observation time points of therapeutic effect indicators, The "Technical Guidelines for Clinical Research on Therapeutic Drugs for Age-Related Macular Degeneration" [30] respectively suggest that "the average letter number change in the improvement of the best corrected visual acuity from baseline as evaluated by the visual acuity table of the Early Treatment of diabetic retinopathy study should be adopted as the primary efficacy endpoint" and "based on the disease progression of nAMD, the characteristics of drug action, etc., Generally, no less than 12 months should be selected as the time point for the primary therapeutic effect evaluation. Therefore, this study selected "the change in BCVA of the study eyes of the two groups of subjects at week 52 compared with the baseline." As the primary endpoint indicator.

4.3 RANDOMIZATION AND MASKING

4.3.1 Randomization

The interactive web response system (IWRS) will be used to randomize subjects in a 1:1 ratio to TAB014 or ranibizumab in this study. The randomization code will be generated by the independent unmasked statistician using SAS software (Version 9.4 or above). The unmasked database builder uploads the subject randomization list and trial drug randomization list into the IWRS system and completes the automatic docking setup between the IWRS and the electronic data capture (EDC) system. Any subject who meets all inclusion criteria and none of the exclusion criteria, will be assigned a randomization number through the IWRS system, which will be recorded by the investigator in the source document. After randomization, which a drug number will automatically be assigned. The study pharmacist will dispense the drug to the subject according to the drug number. A randomization number cannot be reassigned to another patient once it has been used, regardless of drug administration or not.

4.3.2 Masking

Patients, investigators responsible for patient care, vision examiner (including BCVA assessors), research nurses, independent central reading center staff, and the sponsor will be masked. The unmasked statistician or relevant non-project personnel designated by the sponsor shall participate in the masking process. During the randomized double-blind treatment phase, packaged study drug will be provided in a double-blind fashion to maintain the double-blind nature of the study. Since the minimum package of study drugs cannot be completely consistent, unmasked pharmacist, unmasked nurse, unmasked treating investigator and unmasked assistants will take part in this study.

The role of the unmasked treating investigator and any unmasked treating nurses will be specified in the site log. Once assignment is complete, these roles cannot be changed in the study. In order to maintain the masking, the unmasked treating investigator and treating nurses must ensure that the subject will not be exposed to the drug or its packaging before, during, and after the treatment.

The BCVA assessor should not have access to previous VA results of any subject.

To fulfill the masking requirements of the study, the work content and mask setting of the participants are as follows:

Table 2-1 Masking of participants

Participants	Masking wetting	Tasks during the study
Vision examiners (including BCVA assessor)	Masked to treatment assignment	Performs visual acuity (VA) assessment, and provide report to investigator.
Research nurse	Masked to treatment assignment	Assist the investigator with subject care.
Independent central reading center staff	Masked to treatment assignment	Reading images of OCT, FA, CF, ICGA, and provides report.
Investigators responsible for patient care	Masked to treatment assignment	Receive Vision Results; Supervise all assessments (intraocular pressure, slit lamp examination, fundus examination, OCT, CF, ICGA and FFA); Provides treatment decision to treating physician through formal communication.
Treating investigator	Unmasked to the treatment assignment	Responsible for intravitreal injection.
Unmasked Pharmacist, Unmasked Treating Nurse, Unmasked assistant (Limited number)	Unmasked to the treatment assignment	Assist in preparing and performing treatment, conducting drug verification and reviewing drug inventory, etc.

4.4 STUDY PERIODS

This study will be composed of 3 periods: Screening Period, Randomization /Baseline/Frist Treatment, Treatment Period, Final Visit. The overall treatment duration for each patient will be about 12 months.

Screening Period: Day -28 to randomization. After signing the informed consent form, patients will undergo screening tests and data collection for comprehensive evaluation for study eligibility.

Randomization /Baseline/Frist Treatment: First day, the eligibility of study eye needs to be confirmed by the independent reading center, eligible patients will be randomly assigned to the TAB014 or ranibizumab group in a 1:1 ratio, for evaluation of efficacy, safety and immunogenicity in Screening Period. The first dose must treat in randomization day

Treatment Period: Randomization to week 52. Grouped according to randomization, received treatment with TAB014 or ranibizumab.

Final Visit: the week 52, the final visit will be conducted at 4 weeks after the subject's last treatment to evaluate the efficacy and safety, and immunogenicity.

4.5 RETURN OF STUDY DRUG

Preparation of the study drug will be done by designated person from the sponsor and authorized

research institute staff. The accountability, dispensing, return, and disposal of research drug will be defined in the drug Manual. At the end of the trial, delivery record of study drug must be consistent with the quantities of used and destroyed/returned drug. Any discrepancies will be documented and the reason for the discrepancy will be noted in the TAB014 drug Manual.

4.6 EMERGENCY UNMASKING OF TREATMENT ASSIGNMENT

In order to ensure objectivity of the efficacy and safety assessments, researchers who evaluate efficacy and safety parameters will be masked. Electronically encrypted blind codes will be retained by the unmasked statistician and will not be decrypted until the study database is locked.

The sponsor, the investigator responsible for assessment and caring, and the subject will not be informed of the study drug used. Since the packaging of TAB014 is different from ranibizumab, the unmasked pharmacist, the unmasked treating nurse, the unmasked treating investigator, and the unmasked monitor will be involved in this study.

The principle of unmasking in an emergency situation is as follows: The investigator responsible for assessment and caring should not attempt to know what study drug the subject is receiving. In case of emergency or if the subject requires rescue, it is necessary to know which treatment the subject received, the site investigator should contact the monitor, the principal investigator and the sponsor to jointly determine whether to unmask immediately. In very urgent cases, the investigator can decide to unmask urgently. After the emergency has been eliminated or controlled, the site investigator should notify the CRA, PI and sponsor of the details as soon as possible.

Emergency unmasking is performed with the aid of "Unmasking the Subject" in IWRS. When randomized subject requires emergency unmasking, the investigator should log in the IWRS system and use the function of "Unmasking the Subject". After entering the reason for unmasking, the investigator will know the actual study drug received by the subject. The IWRS system will record the investigator who submitted the unmasking request, the reason and the time of emergency unmasking. Investigators with emergency unmasking authority should have to complete relevant training before initiating the study.

After emergency unmasking, the investigator will take corresponding measures to treating and caring subjects according to routing experience. The unmasked subject should withdraw from the study and considered a dropout, and the investigator must record the reason for withdrawal.

5 SELECTION AND EXIT OF SUBJECTS

Approximately 488 patients will be enrolled in this study. Study enrollment is competitive, if the enrollment goal has not been achieved, the investigator could re-screen the initial screen failure subjects once as appropriate and reassign a new screening number.

5.1 INCLUSION CRITERIA

Patients need to fulfil all inclusion criteria.

1) Patients must be > 50 years old, male or female;
2) Independent central reading center confirmed active subfoveal or juxtafoveal choroidal neovascularization (CNV) secondary to neovascular age-related macular degeneration in the study eye (Active is defined as the presence of evidence of subretinal/intraretinal fluid, subretinal hyperreflective material, or leakage);
3) BCVA letter score between 15 and 73 (inclusive) by the ETDRS chart during the screening period and baseline;
4) In the study eye is confirmed by Independent central reading center:

a) Total lesion area is ≤ 12 optic disc areas(30mm^2),

b) Fibrosis, scarring or atrophy< 50% of total lesion area, and not involve the fovea centralis,

c) Subretinal hemorrhage involving the fovea centralis, Intraretinal hemorrhage< 4 optic disc areas;

5) Able to understand and personally sign informed consent form.

5.2 EXCLUSION CRITERIA

Patients who meet any of the following exclusion criteria will be excluded from participating in this study.

Ophthalmic Criteria

1) Ophthalmic Treatment history:

a) Intravitreal injection of an anti-VEGF drug (ranibizumab, bevacizumab, aflibercept or conbercept, etc.) in any one eyes, anti-VEGF injection in the past 90 days in the non-study eye; and expect the study eye will not be able to discontinue the anti-neovascular treatment not in this study during the study period, or expect the non-study eye will need anti-neovascular treatment within 30 days after randomization;

b) Prior vitrectomy, panretinal photocoagulation, ocular treatment or laser treatment for the fovea centralis/surgery for nAMD in the study eye; history of corneal transplantation or corneal dystrophy, treatment with verteporfin, external radiation therapy for head or eyes, transpupillary hypertherapy, expected that the above-mentioned treatment will be required during the research period;

c) Prior intra-ocular (including cataract) surgery in the study eye within 90 days of randomization, or surgery to the exterior eye within 28 days of randomization, or expect intraocular surgery (including anterior segment surgery and posterior segment surgery) will be required during the study period;

d) Prior intravitreal injection or implantation of corticosteroids/sustained-release corticosteroid preparations in the study eye in the past 180days before randomization; or prior other ocular corticosteroid injections except intravitreal injection in the past 30 days before randomization; or expect Intravitreal/periorbital corticosteroid injection by to(excluding topical preparations) in study period;

e) PDT (Photodynamic Therapy) in the non-study eye within the past 30 days before screening,

2) Confirmed to have a BCVA on ETDRS chart of < 18 letters during screening in non-study eye during the screen period of baseline period;

3) Myopia more than -8.0 diopters of refractive error in study eye. For patients who have undergone refractive surgery or cataract surgery, refraction must not have been greater than -8.0 diopters prior to surgery;

4) In study eye: a) absence of the crystalline lens (unless there has been artificial lens replacement), b) posterior capsule rupture or coloboma; c) Priori YAG laser posterior capsulotomy within 30 days of randomization;

5) As judged by the investigator, the study eye currently has a) affecting center vision, or b) increase the safety risk to the patient, or c) affect the efficacy and safety evaluation or collection, or d) not cause of nAMD eye diseases surgical or medical intervention;

6) According to the judgment of the independent reading center, the study eye is currently complicated with: a. Central serous chorioretinopathy, or b. Vitreous hemorrhage, or c. CNV

not caused by nAMD, or d. Retinal pigment epithelium tear, macular hole, macular telangiectasia and other macular abnormalities involving the macula, except for neovascular age-related macular degeneration, or e. Non-namd diseases that affect central vision; Inability to obtain photographs in the study eye from media opacity or inadequate pupillary dilation (including cataracts or corneal opacity), which may interfere with tests such as visual acuity and safety assessment, or fundus photography;

7) During the screening period, the study eye had: a) uncontrolled glaucoma (e.g. intraocular pressure > 24 mmHg, after treatment with anti-glaucoma drugs), or b) Accepted external drainage surgery for glaucoma, or c) Late-stage glaucoma or optic neuropathy that affects or endangers the central visual field of the study eye;

8) At the time of randomization, any active intraocular, extraocular, or periorbital inflammation or infection (such as conjunctivitis, keratitis, scleritis, or endophthalmitis) in either eye;

9) A history of idiopathic or autoimmune-related uveitis in either eye

Systemic condition

10) The detection of hepatitis B surface antigen (HBsAg) is positive, and the titer of hepatitis B virus deoxyribonucleic acid (HBV DNA) in peripheral blood is $\geqslant 1 \times 10^3$ IU/mL. If HBsAg is positive and the titer of HBV DNA in peripheral blood is detected, 1×10^3 IU/mL. If the researcher believes that the chronic hepatitis B of the subject is in a stable stage and does not increase the risk of the subject, the subject is eligible for inclusion. Positive for hepatitis C virus (HCV) antibody, positive for nucleic acid RNA, positive for Treponema pallidum antibody, and positive for human immunodeficiency virus (HIV) antibody Poorly controlled hypertension in spite of appropriate therapy, a single systolic pressure measurement of >160mmHg, or 2 consecutive measurements with diastolic pressure >100mmHg;

11) Poorly controlled hypertension in spite of appropriate therapy, a single systolic pressure measurement of >160mmHg, or 2 consecutive measurements with diastolic pressure >100mmHg;

12) Diabetic subjects with glycated hemoglobin >10%

13) At the time of randomization, the presence of any uncontrolled clinical conditions (e.g., severe psychiatric, neurological, metabolic, immunological, cardiovascular, respiratory, and other systemic diseases, as well as malignant tumors). Individuals with abnormal liver or kidney function (ALT, AST $\geqslant$ 2.5 times the upper limit of the normal range(ULN)). Individuals with total bilirubin $\geqslant$ 1.5 times ULN; creatinine (Crea), urea, or blood urea nitrogen (BUN) $\geqslant$ 1.2 times ULN; or coagulation function abnormalities (prothrombin time > 3 seconds above ULN or activated partial thromboplastin time > 10 seconds above ULN). Those who have experienced any of the following cardiovascular events within 180 days prior to randomization, and which, in the investigator's judgment, may affect patient safety assessment or increase subject risk: myocardial infarction, unstable angina, history of coronary revascularization, history of cerebrovascular accident (including TIA), history of other thromboembolic diseases (such as thromboangiitis obliterans, pulmonary embolism, portal vein thrombosis, etc.), New York Heart Association (NYHA) Class $\geqslant$ II heart failure, or severe unstable ventricular arrhythmias.

14) Prior significant allergic reactions to biological products, or known allergic reactions to bevacizumab, ranibizumab, or study related medication (including fluorescein or indocyanin green), pupillary dilating agents, anesthetic used by the patient during the study period, or anti-infective agents;

15) Systemic anti-VEGF therapy within 90 days prior to randomization is not permitted. However, the use of dietary supplements, vitamins, or minerals is allowed;

16) Randomized within 90 days of continuous systemic corticosteroid use for ≥30 days, or systemic corticosteroid use within 5 days prior to randomization; or anticipated need for systemic corticosteroid use during the study period (intranasal, inhaled, topical skin, intra-articular, perianal corticosteroids, and short-term (continuous use <2 weeks) oral corticosteroids are permitted).

17) Necessity to continue use of prohibited agents (drugs known to be toxic to the lens, retina, or optic nerve, including deoxyamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, ethambutol);

18) Participate in any interventional clinical trial involving pharmacological or medical device treatment (except vitamins and minerals) within 90 days prior to randomization is not permitted, and Use of any other investigational drugs, biologics, or non-approved medical interventions (e.g. isovolemic hemodilution or intravitreal tissue plasminogen activator) during the study period is strictly prohibited, except for study-specific interventions outlined in this protocol;

19) Pregnant or breastfeeding women, or subjects (both male and female) who plan to become pregnant or father a child during the study period or within 6 months after study completion. Female patients with fertility who tested positive in pregnancy tests during the screening period or were unwilling to use reliable contraceptive methods during the study period, including: Hormonal methods for oral, implanted, injectable, or transdermal; Barrier methods with spermicide (diaphragm or condom + spermicide); Intrauterine device (IUD); Surgical sterilization of the male partner;

20) Other conditions that are considered not acceptable by the investigator.

5.3 SELECTION OF STUDY EYE

Only one eye can be selected as study eye for each subject in the study. If both eyes of the subject meet enrollment criteria, it is recommended to select the study eye according to the following principles:1. When both eyes were treated with or without anti VEGF therapy, the eyes with poor vision were selected as the study eye, 2.When one eye was treated with anti VEGF and the other eye was not treated with anti VEGF, the eye that was not treated with anti VEGF was selected as the study eye If the visual acuity is same in both eyes, the eye with better potential for visual acuity improvement will be chosen as the study eye by the investigator (if the visual acuity is the same in both eyes, the eye with the clearest lens and ocular media and the smallest area of subfoveal scar or geographic atrophy can be selected. If there is a lack of objective basis for the study eye selection, the selection should be based on factors such as dominant eye, other ocular lesions, and subject preference). The selection process of the study eye must be documented in the source documents.

5.4 DROP OUT EARLY/TERMINATION INTERRUPTED

5.4.1 Drop Out Early

Subjects need to withdraw in the following situations:

（1） The sponsor terminates the study;

（2） Death;

（3） Lost to follow-up；

（4） The subject withdrew informed consent；

（5） Regulatory authorities or Ethics Committee request for study termination.

The subject can withdraw from the study at any time, and for any reason. Once that decision is made, the investigator should record all information related to withdrawal in the original files and eCRF and medical records (at least including the exit date and the reason).

For patients failing to follow up visits, the investigator should do their best to obtain the general and ophthalmic health status of the subjects. Assessments should be performed according to the items of the Final visit in the flowchart. All communication must be recorded in the patient's medical record.

5.4.2 Treatment Interrupted

Treatment interrupted include: suspend of treatment or termination of treatment. Any treatment interruption must be recorded in original files and the dosing record of eCRF.

Suspend of treatment or termination of treatment by ocular adverse events:

If a subject had an adverse event in the study eye during the course of receiving study treatment, **Appendix 1:** Criteria for Treatment Discontinuation Due to Ocular Adverse Events were used to determine whether treatment needed to be discontinued due to adverse events.

If the investigator decides to suspend treatment, the original medical record shall be recorded, indicating the date of suspension of study treatment and the main reason. In the follow-up, the investigator can judge whether to resume the administration. After the suspension, if the research doctor decides that the administration cannot be resumed, the treatment should be permanently stopped (terminated). If the treatment is terminated, the subject should withdraw from the study and invite the subject to accept all assessments at the final visit as far as possible.

Termination of treatment by non-ocular adverse events:

In addition to **Appendix 1:** Criteria for Treatment Discontinuation Due to Ocular Adverse Events, which requires termination of treatment, the following situations must also require termination of study treatment:

- The following adverse events occurred: cerebral apoplexy or transient ischemic attack, pregnant；
- According to the measures taken for prohibited drug treatment in Table 3-1 (see section 6.2.10 prohibited drugs / treatments), the use of prohibited treatment leads to any other protocol deviation with important safety risks for the subject, and the study needs to be stopped;
- The subjects with accidental unblinding for any reason；
- Intolerable AE that cannot be controlled by symptomatic treatment or delayed dosing;
- Worsening disease based on investigator judgement;
- Termination can maximize the benefit of subjects judged by investigator;
- The subject requested withdrawal;

6 TREATMENT

6.1 STUDY DRUG

Investigational drug: TAB014 Monoclonal Antibody Injection (Recombinant humanized anti-VEGF monoclonal antibody, manufactured by BIODLINK and provided for free) is a sterile solution for injection in a strength of 5mg/0.2mL per vial. It should be stored in a refrigerator at 2-8ºC (36-46ºF), do not freeze, and should be protected from light, with a shelf life of 24 months. Store in light tight closed carton prior to use. Do not use after the date marked on the label. The dose of TAB014 is 1.25mg per intravitreal injection, once every 4 weeks. A total of 13 doses has

been planned for administration during the study.

Control drug: Ranibizumab Injection (Lucentis®, manufactured by Novartis, provided by BIODLINK for free), 10mg/mL, 0.2mL/vial. Store 2-8ºC away from light and do not freeze. The shelf life is 36 months. The dose of ranibizumab (Lucentis®) is 0.5mg per intravitreal injection, once every 4 weeks. A total of 13 doses has been planned to be administered during the study.

6.2 STRUDY TREATMENT

6.2.1 Screening number

The screening number consists of 5 digits, including the center numbers (2 digits) in which the treatment is received, and the consecutive numbers (3 digits) in which the patient signs the informed consent form. The center numbers will be assigned by the sponsor.

At each site, the first patient is assigned number 001, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned number 002, the third patient is assigned number 003).

The screen number will not be reused once assigned to the patient. If a patient is re-screened, a new screen number will be assigned. If the patient fails to be randomized for any reason, the reason should be recorded on the EDC (for data to be collected on screening failures refer to Section 6.3).

6.2.2 Dispensing the study drug

The sponsor will supply study drug to each site and the treating investigator will select the drug to dispense to the subject based on the drug number obtained from the IWRS. The account information of the randomization system can only be managed by the account owner, so as to ensure that all the masked staff can maintain complete mask.

6.2.3 Handling of study treatment

The investigator or site should establish a study drug management system, which should meet the following requirements:

（1） A designated staff shall be responsible for receiving the study drugs and materials (such as unmasked pharmacists, etc.) provided by ZHAOKE;

（2） The receipt, store, distribution and use of the study drugs and materials should be completely recorded;

（3） Study drugs and materials shall be reasonably and safely stored;

（4） Study drugs can only be accessed by the principal investigator or assistants authorized by the principal investigator;

（5） Study drugs can only be treated to randomized subjects according to the protocol;

（6） The investigator should retain unused drugs and the empty packages/ vial of used drugs for inspection and return by the unmasked monitor.

Medication labels will be prepared in accordance with Good Clinical Practice (2020), and will include storage conditions for investigational drug and control drug. Preparation of the drug will be done by designated staffs from the sponsor or an authorized institution. The label should include but not limited to drug number, text "For Clinical Trial Use Only", trial number, sponsor name or manufacturer, shelf life, batch number, usage and dosage, storage conditions, etc. Study drug accountability, dispensing, return, and disposal should be defined in Pharmacy Manual. Each vial of study drug should only be used once, and its contents should not be split for use. Study drug must be stored according to the conditions in the medication label.

ZHAOKE (Guangzhou) Ophthalmology pharmaceutical Co., Ltd will provide enough

TAB014/ranibizumab for treatment to complete this study. At the end of this study, study drug shipment records must be consistent with the used and destroyed/returned quantities. Any discrepancies and the reason for the discrepancy will be documented, and will be detailed in the TAB014 Pharmacy Manual.

Drug outer box lable

A Phase III, Randomized, Multicenter, Doubled-blind clinical trial comparing the efficacy and safety of TAB014 and Lucentis® in neovascular age-related macular degeneration (nAMD) subjects Used only in clinical trial Protocol No.：TOT-CR-TAB014-III-01 Drug No.：DXXXXX Clinical Trial Approval No.：2017L04523 Drug name：TAB014/ Ranibizumab Injection Stangth：25mg/mL， 0.2ml Per vial；10mg/mL， 0.2ml Per vial Package：1via/bax, with 2 needles and 1 syrghe attached Batch No.：XXXXX/XXXXX Shelf Life：XXXXXX Dosage and adiministration：50 μL per intravitreal injection, once every 4 weeks Storage conditions：2-8℃，Storage andtransport dark, do not freeze ZHAOKE (Guangzhou) Ophthalmology pharmaceutical Co., Ltd

Drug original package lable

Used only in clinical trial Drug No.：DXXXXX Clinical Trial Approval No.：2017L04523 ZHAOKE (Guangzhou) Ophthalmology pharmaceutical Co., Ltd

6.2.4 TAB014/Ranibizumab(Lucentis®) administration

6.2.4.1 Pretreatment preparation

TAB014/ranibizumab (Lucentis®) should be administered by qualified investigator. Hospitals should have the relevant instruments, equipment and environment required for the diagnosis and treatment of this disease, and ophthalmologists should have the ability to confirm the diagnosis of neovascular age-related macular degeneration, and be experienced in intravitreal injection.

TAB014/Ranibizumab (Lucentis®) must be injected intravitreal under aseptic conditions, including hand disinfection using surgical procedures, sterile gloves, sterile drapes, and sterile eyelid speculum (or similar). Subjects must be given appropriate anesthetic and topical ophthalmic broad-spectrum antibiotics prior to injection. The periocular skin, eyelids, and ocular surface has to be disinfected before injection, and intraocular pressure measured.

It is recommended that investigators should instruct subjects to self-administer antibiotic eye drops for 3 days before and after each injection. The investigator can adjust the duration and frequency of preoperative antibiotic eye drops according to relevant guidelines, evidence-based evidence, and the situation of the subjects.

6.2.4.2 TAB014/Ranibizumab(Lucentis®) preparation and administration

Unmasked staff responsible for treatment are in charge of TAB014/ranibizumab preparation. The

outside of the vial rubber stopper should be disinfected before withdrawal. Using aseptic technique, withdraw the entire (0.2 mL) contents of the vial through an 18G (5 μm) filter needle attached to a 1 mL sterile syringe. The filter needle should not be used for intravitreal injection and must be discarded after withdrawal. The filter needle must be replaced with a sterile 30G needle forintravitreal injection. The air in the syringe must be evacuated until the tip of the syringe core aligns with the 0.05ml line on the syringe. The injection needle should be placed 3.5 – 4.0mm behind the limbus, aligned with the center of the eye, and inserted into the vitreous to avoid horizontal needle insertion. Slowly advance 0.05mL of injection solution (approximately 5 seconds), taking care to change the scleral injection site for subsequent injections. See the TAB014 drug manual or ranibizumab package insert for details.

6.2.4.3 Post-treatment care

After the injection, the Treating Physician must confirm whether the subject can count fingers or see the movement of fingers, to ensure perfusion of the central retinal artery and record the results in the source document and eCRF. On the day of injection, Vital signs and intraocular pressure were measured after injection and evaluated by the evaluation doctor. Patients should be instructed to self-administer antibiotic eye drops to the study eye 3 days after the intravitreal injection of TAB014/ranibizumab. Additional information regarding the administration of TAB014/ranibizumab including precautions can be found in the TAB014 drug handbook or Lucentis® package insert.

6.2.5 Treatment regimen for the study eye

Subjects will be treated at every 4-week visit over a period of 12 months (see assessment schedule in Table 1-1). If the treatment is not administered, the patient must still be scheduled for the next visit according to the protocol.

TAB014/ranibizumab (Lucentis®) will be administered to the subjects in a volume of 0.05ml by a qualified ophthalmologist according to the randomization number. TAB014/ranibizumab (Lucentis®) will be administered by intravitreal injection every 4 weeks at the standard dose of TAB014 1.25 mg/0.05 mL and ranibizumab (Lucentis®) 0.5 mg/0.05 mL for a total of 13 injections. The interval between doses should not be shorter than the time interval (14 days) in the flow chart.

6.2.6 Treatment of the non-study eye

Subjects who develop an ocular disorder in the non-study eye which in the opinion of the investigator requires treatment during the study, may be treated at the investigator's discretion, with the exception of medications and treatments that are not allowed by the protocol. If the non study eye is diagnosed with nAMD, the investigator will give symptomatic treatment at his discretion, but the treatment must not be earlier than 30 days after randomization.

To avoid the potential increased risk of systemic adverse events caused by the injection interval between the two eyes being too close, the injection of anti-VEGF drugs in the non-study and study eyes should not be carried out simultaneously. The injection interval should be extended as much as possible based on the researcher's judgment without delaying the treatment of the contralateral eye. As the treatment plan for the study eye in this study is once every 4 weeks, it is recommended that the interval between anti-VEGF injections for the non-study eye and the study eye be 14 (±3) days.

Treatment of the non-study eye will be captured in the source document and eCRF. The non-study eye must be observed in routine clinical practice, and AE and SAE must be recorded in the source document and eCRF.

6.2.7 Permitted dose adjustments

The dose injected with TAB014/ranibizumab (Lucentis®) at each treatment visit must not be changed.

6.2.8 Delayed treatment

If the subject's injection exceeds the window at a visit during the treatment period, it is necessary to determine whether to delay the administration according to the time of this time: if the time of

exceeding the window is ⩽ 7 days, the delayed administration is acceptable, and the interval between the injection and the next visit must be ⩾ 14 days.

6.2.9 Concomitant treatment

The investigator should instruct patients to notify the study site about any new medications he/she takes after enrollment into the study. All medications and non-drug therapies (including physical therapy and blood transfusions) administered after the patient started the study must be listed in the concomitant medications/ non-drug therapies in source document and the eCRF (except for routine medications for ocular procedures required by the protocol, i.e. fluorescein, indocyanine green, mydriatics, topical anesthetics (including retrobulbar anesthetics to avoid eye movement), antibiotics for rinsing conjunctival sac before injection, antibiotic eye drops dispensed before and after injection).

6.2.10 Prohibited drug and treatment

1) The following treatments are not allowed in the study eye throughout the entire study:

a) External-beam radiotherapy for eyes and head, focal laser photocoagulation, transpupillary thermotherapy, for nAMD.
b) Intraocular surgery includes anterior chamber surgery and posterior chamber surgery, such as cataract surgery, glaucoma filtration surgery, and vitrectomy, YAG laser posterior capsulotomy, etc.
c) Intraocular/periocular corticosteroids and intraocular corticosteroid implants (e.g., dexamethasone, fluocinonide).
d) Anti-angiogenic drugs (including any anti-VEGF agents e.g., pegaptanib, bevacizumab, aflibercept, conbercept, ranibizumab, brolucizumab etc.) that are not study drugs of this study.
e) Eye drops with indications such as fundus hemorrhage and fundus macular degeneration (such as esculenta digitonin eye drops)

2) The following medications are not allowed in the non-study eye within 30 days after randomization, during the entire study process.

Any anti-angiogenic drugs (including pegaptanib, bevacizumab, aflibercept, conbercept, ranibizumab, brolucizumab etc.) that are not study drugs of this study.

3) The following systemic medications are not allowed throughout the entire study process:

a) Anti-VEGF drugs (e.g. sorafenib, sunitinib, bevacizumab etc.).
b) Chinese patent medicine with indications such as fundus hemorrhage and fundus macular degeneration.
c) Corticosteroids. Intranasal, inhaled, topical skin, intra-articular, perianal steroids and short-term (continuous use < 2 weeks) oral steroids were allowed.
d) Medications known to be toxic to the lens, retina or optic nerve including deferoxamine, chloroquine, hydroxychloroquine, tamoxifen, phenothiazine and ethambutol.
e) Furthermore, any other type of study drug or study intervention (e.g. isovolumic hemodilution, intravitreal tissue plasminogen activator) is prohibited throughout the study.

Table 3-1 Action to be taken for the Prohibited Treatment/Medication

Treatment	Actions to be taken
External-beam radiation therapy, focal laser photocoagulation, transpupillary thermotherapy, vitrectomy, submacular surgery, or other surgical interventions for AMD in the study eye	Discontinue study treatment permanently
Other anti-VEGF drugs (study eye)	Discontinue study treatment permanently

Intra-/peri-ocular corticosteroids (except for topical preparation) in the study eye	Discontinue study treatment permanently
Intra-ocular corticosteroid implants (study eye)	Discontinue study treatment permanently
Other study medicinal products in any eye	Discontinue study treatment permanently
Anti-VEGF agents in the non-study eye within 30 days after randomization in the study eye	No action, but cannot participate in ADA collection
Anterior chamber surgery (e.g., cataract surgery, glaucoma filtration surgery) in the study eye	Discontinue study treatment for 28 days before and after surgery
Posterior chamber surgery (such as vitrectomy) in the study eye	Discontinue study treatment permanently
Systemic use of anti-VEGF drugs	Discontinue study treatment permanently
Systemic use of corticosteroids (Continuous use time >2 weeks)	Discontinue study treatment permanently
Deferoxamine	No action
Chloroquine/hydroxychloroquine	No action
Tamoxifen	No action
Phenothiazines	No action
Ethambutol	No action

6.2.11 Study completion and end of the study

The subject will be considered to have completed the study after the last / withdraw visit has been performed.

The end of the study was defined as the completion of the final visit or loss of follow-up for all subjects.

7 VISIT SCHEDULES AND ASSESSMENTS

Table 1-1 Study flow chart lists all of the assessments and procedures to be performed during study visits. All data obtained from these assessments must be supported in the patient's source document.
The subjects and investigator should make effort to comply with the study visit schedule, and the time window should be kept within ± 7days in this study. If a visit is out of window, the investigator can decide whether to intravitreal injection based on the Subjects' conditions and still be scheduled for the next visit according to the protocol.

7.1 STUDY PROCESS

The investigator should urge subjects to conform to visits as scheduled according to the protocol Table 1-1 . Any visit beyond the visit window is a protocol deviation. The investigator should find out the reasons for exceeding the visit window and take corresponding measures.

7.1.1 Screening period

Screening period: week -4 – 0 week (D-28 to W0 D0).

If the results of examinations performed prior to signing informed consent are within the required timeframe for this study, these tests do not need to be repeated at the screening period.

Before randomization, each potential subject will be checked to determine whether they are eligible for enrollment. Written informed consent must be obtained from the subject prior to any screening activity. Participants who enter the screening period but do not meet the eligibility

criteria are considered screen failure. If the investigator believes that the subject's condition has changed and may meet the eligibility criteria, he can consider re-screening the subject, and the same subject can be screened again at most once.

The following activities should be completed during the screening period:

(1) Sign informed consent form;

(2) Collection of medical history: record includes the medical history of systemic diseases within the 6 months prior to the screening period; record any serious, unstable, uncontrolled systemic diseases; record any history of systemic diseases that may affect the efficacy and safety results of the study; record the history of eye diseases within 2 years prior to the screening period; record any history of ophthalmology diseases that may affect the efficacy and safety results of the study; record the previous drug history within the 6 months prior to the screening period; record the history of systemic surgery and non-pharmaceutical treatment within 6 months before the screening period; record any history of eye surgeries and non-pharmaceutical treatments; record any history of anti-VEGF eye surgery; record any history of allergies; record the history of smoking and drinking.

(3) Collect demographic data, including date of birth, age, gender, ethnicity, and race;

(4) Measure height and weight, and accept the results within 28 days before randomization;

(5) Perform physical examination and measure vital signs. Vital signs include temperature, blood pressure, pulse, respiratory rate. The results of the examination should be within 28 days before randomization.

(6) Laboratory examination, the results of the examination should be within 14 days before the randomization. Blood routine examination includes, red blood cell, white blood cell and platelet count, neutrophil, lymphocyte, eosinophil and basophil count. Blood biochemistry includes sodium, potassium, chloride, glucose, urea/BUN, creatinine, calcium, phosphorus, magnesium, total bilirubin and direct bilirubin, total protein, albumin, ALT, AST, LDH, ALP and uric acid. The coagulati hemoglobin on function includes prothrombin time, INR and APTT. Urine routine includes urine glucose, urine protein, and pH;

(7) The test item for Glycated hemoglobin detection is haemoglobin A1c (HbA1c),the result of the examination should be within 28days before the randomizaition.

(8) Pregnancy test: mandatory for women of childbearing age (blood pregnancy test is not required if one of the following conditions exists: the subject has undergone sterilization surgery such as hysterectomy and/or bilateral oophorectomy, and has no menstruation for 12 consecutive months (Combined with age and other factors, it is judged as menopausal. However, blood pregnancy test is required for patients with bilateral fallopian tube ligation). A blood pregnancy test should be performed within 28 days before randomization.

(9) 12 - lead ECG, chest X-ray examination, results within 14 days before randomization is acceptable.

(10) Chest X-ray examination, results within 28 days before randomization is acceptable. (If the subject has CT results within 28 days before randomization, CT results can be accepted to replace chest X-ray results).

(11) Virological screening: The blood HBsAg, HCV, HIV and syphilis test data within 3 months before randomization can be used. Subjects with positive hepatitis B surface antigen need to undergo HBV-DNA titer or quantitative test; those with hepatitis C virus (HCV) antibody positive need to undergo HCV-RNA test at the same time.

(12) Ophthalmic examination: The results of slit lamp examination, fundus examination, intraocular pressure measurement, OCT examination and BCVA, CF, ICGA, FFA

examination in both eyes within 14 days before randomization are accepted. OCT, intraocular pressure, CF, ICGA and FFA examination suggested that the same subject use the same examination instrument throughout the study period.

(13) Collection of concomitant medication and concomitant treatment.

The results of the screening period will be recorded in the eCRF of each randomized subject. The source documents supporting the results of the screening period must also be kept in the subject's medical records.

7.1.2 Randomization/Base line/ First dose

Randomization/Base line/ First dose: The first day of Week 0, randomization/baseline is defined as day 1. The first dose must be given on the day of randomization, and the rest of the treatment visits have a time window of ± 7 days.

After obtaining the informed consent of the subjects, completing all necessary steps of the screening period, and the investigator believes that the subjects meet the Enrollment Requirements of the study, they can be randomized.

All qualified subjects must be randomly grouped in a 1:1 ratio through the randomization system. The randomization stratification factor is the PCV of the study eye (determined as yes or no by the independent reading center); the BCVA of the study eye at the baseline (< 24 letters or ⩾24 letters).

If the screening period and the randomization/baseline/first dose of the study procedure are repeated and have the same requirements for the number of days before randomization, the study procedure can be conducted only once during the screening period and at baseline (e.g. laboratory examinations are both in screening period and baseline, and the results of the laboratory examinations during both the screening period and the baseline were accepted within 14 days before randomization, then the laboratory examinations can be performed only once during the screening period and the baseline.

The following activities should be carried out During randomization/base line/ first dose:

(1) Physical examination and measurement of vital signs, including temperature, blood pressure, pulse, respiratory rate. Vital signs should be checked before injection (within 24 hours) and 60 (± 30) minutes after injection, and physical examination should accept the results of 7 days before randomization.

(2) Laboratory examination, the results of the examination should be within 14 days before the randomization: blood routine examination includes hemoglobin, red blood cell, white blood cell and platelet count, neutrophil, lymphocyte, eosinophil and basophil count. Blood biochemistry includes sodium, potassium, chloride, glucose, urea/BUN, creatinine, calcium, phosphorus, magnesium, total bilirubin and direct bilirubin, total protein, albumin, ALT, AST, LDH, ALP and uric acid. The coagulation function includes prothrombin time, INR and APTT. Urine routine includes glucose, protein, and pH.

(3) 12 - lead ECG, chest X-ray examination, results within 14 days before randomization is acceptable.

(4) Ophthalmic examination: the results of Slit lamp examination, fundus examination, intraocular pressure measurement, OCT examination in both eyes within 14 days before randomization are accepted. The result of BCVA examination in both eyes, within 3 days before randomization are accepted. OCT,intraocular pressure examination suggested that the same subject use the same examination instrument throughout the study period.

(5) The result of CF, ICGA, FFA examination in both eyes on baseline within 14 days before randomization are accepted.

(6) Immunogenicity test: The subjects undergoing immunogenicity testing had their blood drawn within 2 hours before administration, with 5mL of blood collected.

(7) Assessment after inject: Measure the intraocular pressure of both eyes after each administration of TAB014/ ranibizumab (Noxide ®) within 60 (±10) minutes after injection.After the injection, check whether the subject's research eye can count fingers or see the movement of fingers clearly (within 15 minutes after the injection and administration, conduct digital inspection at 1 meter. If the subject cannot count fingers correctly at 1 meter, conduct inspection at 2/3 meters. If the subject still cannot count fingers correctly, conduct inspection at 1/3 meters, and record the distance of digital vision. If the subject still cannot count fingers at 1/3 meters, conduct manual inspection at 2/3 meters, if it still cannot be manually, conduct manual inspection at 1/3 meters. If the subject does not have manual vision, conduct light perception inspection), to ensure that the central retinal artery has blood perfusion, and records. If there is no safety problem 60 minutes after each treatment, the subject can leave.

(8) Collection of concomitant medication and concomitant treatment.

(9) Collect adverse events.

The results of the randomization / baseline / first dose examination will be recorded in the ECRF of each randomized subject. The source files supporting the results of the randomization / baseline / first dose examination must also be kept in the subject's medical records.

7.1.3 Treatment Period

Treatment period: randomization –week 52. A time window of ± 7 days allowed for each treatment visit (Table 1-1). Before each visit administration, investigator should confirm that the conditions for administration are met before prescribing, then give the study drug.

If a subject experiences an adverse event while receiving study treatment, treatment interruption is allowed and may subsequently be resumed at the discretion of the investigator. If treatment is interrupted, arrange subject for next visit.

During the treatment, the following activities should be carried out:

(1) Vital signs: Vital signs should be checked before injection (within 24 hours) and 60 (± 30) minutes after injection

(2) Physical examination: The result should be 7 days before each administration. It is carried out before dosing at week 12, 24, 36 as indicated in the flowchart.

(3) Laboratory examination: The result should be 7 days before each administration. It is carried out before dosing at week 12, 24, 36 as indicated in the flowchart.

(4) 12 - lead ECG: The result should be 7 days before each administration. It is carried out before dosing at week 12, 24, 36 as indicated in the flowchart.

(5) Slit lamp examination: A slit-lamp examination of both eyes was performed within 3 days prior to each visit.

(6) Fundus examination: A fundus examination of both eyes was performed within 3 days prior to each visit.

(7) OCT examination: A OCT examination of both eyes was performed within 3 days prior to each visit. OCT examination suggested that the same subject use the same examination instrument throughout the study period.

(8) Intraocular pressure measurement is performed on both eyes 3 days before drug administration at each visit. Intraocular pressure examination suggested that the same subject use the same examination instrument throughout the study period.

(9) BCVA examination is performed on both eyes according to the ETDRS form within 3 days before administration at each visit.

(10) CF, ICGA and FFA examination are performed on both eyes. FFA, CF, ICGA and FFA examinations were performed on both eyes at the week 12, 24. The results were received within 28 (±7) days after administration at week 8 and within 28 (±7) days after administration at the week 20, respectively. For the same subject, it is recommended to use the same examination instrument for CF, ICGA and FFA throughout the study period.

(11) Immunogenicity test: The subjects undergoing immunogenicity testing had their blood drawn within 2 hours before administration, with 5mL of blood collected.

(12) Assessment after inject: Measure the intraocular pressure of both eyes after each administration of TAB014/ ranibizumab (Noxide ®) within 60 (±10) minutes after injection.After the injection, check whether the subject's research eye can count fingers or see the movement of fingers clearly (within 15 minutes after the injection and administration, conduct digital inspection at 1 meter. If the subject cannot count fingers correctly at 1 meter, conduct inspection at 2/3 meters. If the subject still cannot count fingers correctly, conduct inspection at 1/3 meters, and record the distance of digital vision. If the subject still cannot count fingers at 1/3 meters, conduct manual inspection at 2/3 meters, if it still cannot be manually, conduct manual inspection at 1/3 meters. If the subject does not have manual vision, conduct light perception inspection), to ensure that the central retinal artery has blood perfusion, and records. If there is no safety problem 60 minutes after each treatment, the subject can leave.

(13) Collect adverse events.

(14) Collection of concomitant medication and concomitant treatment.

7.1.4 Final Visit

On the 1st (±7) day of week 52. The subjects need to undergo the final visit. The following activities should be carried out during the final visit

(1) Vital signs;
(2) Physical examination;
(3) Laboratory examination;
(4) Blood pregnancy test: applicable to female subjects of childbearing age. During the study period, the investigator may decide whether to conduct additional pregnancy tests.
(5) 12 - lead ECG;
(6) Chest x-ray;
(7) Slit lamp examination;
(8) Fundus examination;
(9) OCT examination is performed on both eyes and suggested that the same subject use the same examination instrument throughout the study period.
(10) Intraocular pressure measurement is performed on both eyes. Intraocular pressure examination suggested that the same subject use the same examination instrument throughout the study period.
(11) BCVA examination is performed on both eyes.
(12) CF, ICGA and FFA examination are performed on both eyes For the same subject, it is recommended to use the same examination instrument for CF, ICGA and FFA throughout the study period.
(13) Collect adverse events.
(14) Collection of concomitant medication and concomitant treatment.
(15) Immunogenicity test: For subjects undergoing immunogenicity test, 5mL of venous blood was collected 28 (±7) days after the last administration.

7.1.5 The final visit for early withdrawal or termination of treatment

Regardless of the reason, when a subject require early withdrawal or discontinuation of treatment, investigator should make every effort to obtain information on the subject's general health and ocular condition. Within 4 weeks after the last administration, the subject should be assessed as closely as possible according to the last visit procedures outlined in Table 1-1 (Study Flowchart)

7.1.6 Unscheduled Follow-up

During the trial, for the safety of the subjects, if the subject has an AE or abnormal laboratory examination, or the non-study eyes of the subjects received anti-VEGF drug treatment. the investigator can increase the number of follow-up visits according to actual needs, and that is unscheduled follow-up. The investigator must record the subjects' unscheduled follow-up in the source documents etc. The following are routine items: (If necessary, the investigator can increase/decrease the inspection items.)

(1) Record the symptom complaint;

(2) Vital signs and physical examination (according to actual needs);

(3) Eye examinations, such as slit lamp examination, fundus examination, OCT examination, intraocular pressure measurement and BCVA, CF, ICGA, FFA examination, etc. (according to actual needs);

(4) Laboratory inspection (according to actual needs);

(5) 12 - lead ECG and other corresponding auxiliary examinations (according to actual needs);

(6) Record adverse events;

(7) Record concomitant medication and concomitant treatment;

(8) Make an appointment for the next follow-up visit.

7.2 INFORMATION TO BE COLLECTED ON SCREENING FAILURES

Patients who are screened but not eligible for study are considered screen failures. The reason for this must be documented on the Screening Log. In addition, for all subjects who fail screening, the date of signing the ICF, demographic information and screening data completed in the screening period will be collected in the eCRF, and the reasons for screen failure must be recorded.

7.3 PATIENT DEMOGRAPHICS/MEICAL HISTORY

Demographic/other baseline characteristics will be collected for all randomized subjects as shown in Table 1-1, including:

date of birth, age, gender, ethnicity, race, etc.;

Collection of medical history: record includes the medical history of systemic diseases within the 6 months prior to the screening period; record any serious, unstable, uncontrolled systemic diseases; record any history of systemic diseases that may affect the efficacy and safety results of the study; record the history of eye diseases within 2 years prior to the screening period; record any history of ophthalmology diseases that may affect the efficacy and safety results of the study; record the previous drug history within the 6 months prior to the screening period; record the history of systemic surgery and non-pharmaceutical treatment within 6 months before the screening period; record any history of eye surgeries and non-pharmaceutical treatments; record any history of anti-VEGF eye surgery; record any history of allergies; record the history of smoking and drinking.

7.4 TREATMENT EXPOSURE AND COMPLIANCE

Information regarding study drug administration will be collected in the source document and eCRF. Treatment compliance of the study eye will be assessed by comparing the number of doses.

7.5 EFFICACY ASSESSMENT

Efficacy assessments will include both functional (BCVA) and anatomical evaluations (CF, ICGA, FFA and OCT). The methods of evaluation and parameters to be assessed are described below.

Study eye:

The eye meeting the eligibility criteria at screening is the study eye. If both eyes meet the conditions, If both eyes meet the conditions, the investigator determines the study eye according to the criteria listed in the selection of the study eye in Section 5.3. The selection process of the research eye needs to be recorded in the source file. The study eyes will be treated and the efficacy of the study will be evaluated. The assessment schedule is outlined in Table 1-1 and all results will be documented on source document and eCRF.

Non-study eye:

The non-study eye will be assessed according to the items and time points listed in Table 1-1 and the results will be recorded in the source document and eCRF. In addition, if the non-study eye is diagnosed with nAMD during the study and is treated at the investigator's discretion, the corresponding visit should be entered in the eCRF (including BCVA assessment). Any other non-protocol required efficacy assessments performed at the discretion of the investigator during the study will be collected in source documents only.

7.5.1 Visual Acuity assessment

Visual acuity will be evaluated in the study and non-study eyes using the ETDRS chart according to the visit points specified in Table 1-1 to be done without pupillary dilatation. Here are a total of 14 lines of 5 letters each, with an inspection distance of 4 m. The first line of the largest letter was identified verbatim, and the word identification 1 was 1 point. If the number of letters correctly read at 4 meters is ≥20 letters, the BCVA score is the total number of letters correctly read at 4 meters plus 30, which is counted as the sum; if the number of letters correctly read at 4 meters is < 20 letters, the BCVA score is the sum of the number of letters(Read only the above 6 lines) correctly read at 4 meters and 1 meter; if there is no correctly identified letter at 4 meters and a meter distance examination, the visual acuity score is 0; and the visual acuity score at 4meters distance can reach up to 100 points. If the subject correctly reads 0 letters at 1 meter, the subject should have counting, manual, or light perception vision tests. Further details of refractive and visual acuity testing are described in the "Standard Operating Manual for Standardized Optometry and Best Corrected Visual Acuity".

Best-corrected visual acuity assessments will be performed according ETDRS chart that will be maintained in the source documents, while BCVA scores will be recorded in the source documents and eCRF.

For the training and certification of ETDRS assessment technicians, as well as the certification of ETDRS testing environments and equipment, please refer to the "Standard Operating Manual for Standard Optometry and Best Corrected Visual Acuity".

7.5.2 Color fundus photography, indocyanine green angiography and fluorescein angiography

CF, ICGA and FFA will be performed according to the Table 1-1 If ICGA and FFA examinations were performed within 7 days prior to randomization as part of routine clinical practice (e.g., diagnostic procedures) and met the ICGA and FFA examination requirements described in this protocol and in the Independent Central Reading Center section of the Study Operations Manual, the examination results were acceptable as baseline examination results. It is recommended that the same subject use the same CF, ICGA and FFA examination instruments, and the result keep two decimal places.

The investigator should ask the subjects about drug allergy history and systemic history in detail,

inform the subjects of relevant matters of angiography, and then the subjects should sign the informed consent form for fundus angiography examination; all the subjects strictly follow the requirements of skin test, and those who are not allergic to contrast agent will conduct ICGA and FFA to determine the type of AMD.

ICGA and FFA will be performed after color fundus (CF) photography as shown in Table 1-1 to assess choroidal and retinal vessels. Macular edema, leakage, neovascularization, and lack of perfusion will be recorded in the source documents and the eCRF. Refer to the Study Operations Manual for further procedural details.

7.5.3 Optical Coherence Tomography

Optical Coherence Tomography (OCT) images are to be obtained using Spectral Domain (SD) optical coherence tomography (OCT) equipment. For consistency of the OCT data, the same HD/SD-OCT device is recommended for an individual patient throughout the study, and the result keep two decimal places.

The investigator must perform OCT examination at visits according to Table 1-1. The information collected will be used by the investigator to assess the status of disease activity and recorded in the source document and eCRF.

To fully evaluate retinal details, and to monitor the effects of treatment on the lesion, the investigator must use the high resolution scans to obtain the required OCT data. Refer to the Study Operations Manual for further procedural details.

7.5.4 Independent Central Reading Center

The independent central reading center(IRC) for this study is Mairui (Jiaxing) Medical Technology Co., LTD.

The images of CF, ICGA, FFA and OCT will be sent by the study sites to the IRC of this study. According to the requirements of the protocol, the images of CF, ICGA, FFA and OCT will be evaluated by the IRC at week 0, 12, 24 and week 24. During the study period, CF, ICGA, FFA, CF and OCT images sent to IRC would mask the identity information of the subjects. Technicians or photographers conducting CF, ICGA, FFA and OCT evaluations need to receive training and certification from IRC. Only after passing the certification can they carry out research, and they must remain blinded during the research period. Before the research begins, the brands and models of the equipment in each center will also be collected to ensure that the film reading systems of the independent film reading centers can accurately identify them. For information on how to label, save and transfer images to IRC, as well as the handling of questions and the evaluation methods of various indicators, please refer to the center's imaging documents such as the "Imaging Procedure Manual" and the "Certification Manual".

The original files and a digital copy of the CF photographs, ICGA, FA, CF and OCT images will be stored with the source documents at each study center.

7.5.5 Appropriateness of efficacy measurements

Assessment of BCVA using ETDRS is standard in clinical trials evaluating ophthalmic conditions.

OCT is a non-invasive procedure that uses optical interferometry to visualize the structures within the retina. It is widely used in clinical practice to evaluate the retina in patients with AMD or other retinal diseases.

FFA is a standard assessment in clinical practice for evaluating the retinal vasculature.

As PCV lesions arise from the choroidal vasculature and the associated vascular abnormalities develop beneath the RPE, they exhibit numerous clinical and pathological similarities with AMD. In many instances, differentiating the PCV subtype solely based on FFA proves challenging. Given that ICGA utilizes light with a longer wavelength than fluorescein dyes, it enables deeper visualization of leaking choroidal vessels that may remain inconspicuous on FFA. Consequently,

ICGA plays a pivotal role in the accurate differential diagnosis of PCV subtypes.

7.6 SAFETY EVALUATION

Safety evaluation includes vital signs, physical examination, laboratory examination, electrocardiogram (ECG), Ocular and non-ocular adverse events, serious adverse events (SAEs), adverse events of special interest (AESI), etc., which are appropriately MedDRA(Version 25.0 or above) coded. Accroding to **Appendix 3 STAGING SCALE FOR OCULAR ADVERSE EVENTS**

In accordance with Appendix 3: Ocular Adverse Event Classification Table and the NIA Guidelines for Adverse Events and Serious Adverse Events (September 2018 Edition), ocular and non-ocular adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) were systematically classified. Correlation assessments were performed to evaluate potential associations with the investigational product, followed by drug-related causality assessments. All findings were meticulously documented.

Safety assessments will be performed at the time points of the flow chart and recorded in the source document and eCRF.

7.6.1 Physical examination

Physical examination will be conducted as indicated in Table 1-1 and recorded in the source document and eCRF.

7.6.2 Vital signs

Vital signs evaluations at each visit include blood pressure (systolic and diastolic in mmHg), pulse rate (beats/minute), temperature (Celsius), and respiratory rate (breaths/minute). The above measurement results are recorded in the source documents and ECRF

7.6.3 Height and weight

Height (cm, to the nearest 0.1cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at screening period and recorded in the source document and eCRF.

7.6.4 Ophthalmic examinations

Ophthalmic examinations for safty evaluation include slit lamp examination, intraocular pressure measurement, and fundus examination (Optic disc, macula, peripheral retina, retinal vessels). At each visit and before TAB014/ranibizumab(Lucentis®) treatment, examinations must be performed according to Table 1-1. Slit-lamp examinations are required for both eyes during the screening period, before each administration and at post-treatment visit (Premature withdrawals: 4-week post-dose follow-up). Fundus examinations are performed for the study eye during the screening period, before each administration and at post-treatment visit. Binocular fundus examination during the screening period, before each administration. Binocular intraocular pressure measurement during the screening period, before each administration and at the final visit. A non-contact tonometer was used for intraocular pressure measurement. The investigator will evaluate whether abnormal findings are clinically significant and document them in the source documents and eCRF. Any clinically significant abnormalities of either eye will be recorded either in the medical/ocular history eCRF or in the Adverse Event eCRF depending on when the abnormality occurs.

After treatment evaluation: Intraocular pressure (IOP) will be assessed in the both eyes after treatment with TAB014/ranibizumab (Lucentis®). IOP values (mmHg) will be recorded in the source document and eCRF. In addition, as part of the post-injection safety assessment, after the injection check whether the subject can count fingers or see the movement of the fingers (15 minutes after the injection, perform a figure counting examination at 1 meter. If the subject can't count fingers correctly at 1 meter, check at 2/3 meters. If subjects still can't count fingers correctly,

check at 1/3 meter and record the distance of finger's vision. If at 1/3 meter the subject still cannot count the fingers, perform a hand movement test at 2/3 meters. If the subject has no manual vision, perform a light perception test) to ensure that the central retinal artery has blood perfusion and record it. If no safety issues occur 60 minutes after each treatment, the subject can leave. If it still does not return to normal, please continue to review until it returns to normal or take necessary measures. Any safety issues should be dealt with by the investigator.

7.6.5 Laboratory evaluations

Laboratory evaluations: Laboratory evaluations is including Blood routine examination, blood biochemical examination, coagulation function test and routine urine test. Blood routine examination includes hemoglobin, red blood cell, white blood cell and platelet count, neutrophil, lymphocyte, eosinophil and basophil count. Blood biochemistry includes sodium, potassium, chloride, bicarbonate, glucose, urea/urea nitrogen, serum creatinine, calcium, phosphorus, magnesium, total bilirubin and direct bilirubin, total protein, albumin, ALT, AST, LDH, ALP and uric acid. The coagulation function includes prothrombin time, INR and APTT. Urine routine includes urine glucose, urine protein and pH; Examination results should be recorded in the source document and eCRF.

7.6.6 12 - lead ECG

12-lead ECG will be conducted as shown in Table 1-1， evaluated by investigator and recorded in the source document and eCRF. An 18-lead ECG may be conducted in lieu of a 12-lead ECG when the investigator determines it clinically indicated.

7.6.7 Pregnancy and assessments of fertility

For female subjects of childbearing potential (blood pregnancy test is not required in case of one of the following conditions: the subject has undergone sterilization surgery, such as hysterectomy and/or oophorectomy, and has no menstruation for 12 consecutive months (it is determined to be postmenopausal in combination with age and other factors). However, blood pregnancy tests are required in patients with tubal ligation.), blood pregnancy tests should be performed within 28 days before randomization and the Final visit. Additional urine pregnancy tests may be performed during the study at the discretion of the investigator.

7.6.8 Appropriateness of safety evaluation

The safety evaluation indicators selected in this study include physical examination, vital sign examination, ophthalmological examination, laboratory examination, 12-lead ECG, chest radiograph, pregnancy test, etc., all of which are routine clinical examination items, in order to guarantee the benefits as much as possible.

7.7 IMMUNOGENICITY EVALUATION

Immunogenicity blood collection will be performed in 80 subjects with nAMD in one eye and no who have not received anti-VEGF therapy in both eyes or the contralateral eye throughout the study period in accordance with Table 1-1 before administration at. week 0, week 12, week 24 and at final visit. The blood collection points in treatment period are within 2 hours before each administration. The last blood collection point in final visit isconsidered as 28 (±7) days after the last administration, and record in eCRF, 5 mL blood iscollected each time. The collection and processing, labeling, storage and transportation procedures of immunogenic samples are detailed in the central laboratory manual. For samples that test positive for ADA in the confirmation test, titer tests and neutralizing antibody activity tests need to be conducted.Positive immunogenicity is defined as a negative baseline ADA and a positive ADA result after treatment, or a positive baseline ADA and a titration of samples with positive ADA after treatment at least a 4-fold increase from baseline.

8 ASSESSMENT OF SAFETY

8.1 ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered study drug and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product， whether ornot considered related to the medicinal product.

Occurrence of adverse events should be determined by open questions at each visit during the study. Adverse events may also be reported by the subject during or between visits or detected by physical examination, laboratory examinations, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- induce clinical signs or symptoms
- are considered clinically significant
- require therapy

Adverse events include the following situations:

- The original (prior to receiving the investigational drug) medical condition/aggravation of the disease (including symptoms, signs, aggravation of laboratory abnormalities)
- Any newly occurring adverse events: Any newly occurring adverse medical condition (including symptoms, signs, newly diagnosed diseases)
- clinically significant abnormal laboratory values or results of clinical significance, and not caused by concomitant diseases

The natural physiological state of human body and expected medical events are not AES, such as women's menstruation and established surgical arrangements. In addition, adverse events also include symptoms, signs or abnormal laboratory tests caused by the following reasons, drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependence, drug spillover, pregnancy events.

After signing the informed consent, the events that occurred before receiving the trial drug will not be regarded as AES, but should be recorded in the medical history.

For all adverse events, the investigator should obtain sufficient information to determine the cause of the adverse event and evaluate the cause of the adverse event. The investigator must follow up until the adverse event or its sequelae are eliminated or stabilized at an acceptable level for the investigator, as well as abnormal laboratory tests that the investigator believes are no longer of clinical significance or the subject is lost to follow-up.

8.1.1 Serious Adverse Event (SAE)

An SAE is any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria：

1) fatal
2) life-threatening (It refers to that the subject is at risk of death when the adverse event occurs, not assuming that the adverse event will be aggravated and the subject is at risk of death if not treated)
3) results in persistent or significant disability/incapacity
4) constitutes a congenital anomaly/birth defect
5) Causing hospitalization or prolonged hospitalization, except for prolonged hospitalization

or prolonged hospitalization caused by the following reasons

a) routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

b) elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

c) treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

d) social reasons and respite care in the absence of any deterioration in the patient's general condition

6) It is of great medical significance, that is, it is defined as an event that endangers the subject, or may require drug or surgical intervention to prevent one of the above results.

All malignant tumors will be assessed as adverse event under "medically significant" if other seriousness criteria are not met.

8.1.2 Suspicious and unexpected serious adverse reactions(SUSAR)

SUSAR refers to the suspicious and unexpected serious adverse reactions whose clinical manifestations are beyond the existing information, such as the experimental drug researcher's manual, the instructions of listed drugs or the product characteristic summary.

8.1.3 Adverse Events of Special Interest

Special attention should be paid to the possible adverse reactions of TAB014. If the following adverse events occur in this study, they will be classified as adverse events of special concern (AESI)

- Ocular AESI include:
  - Infectious endophthalmitis
  - Non-infectious endophthalmitis (e.g. Iritis, Vitritis and Iridocyclitis)
  - Elevated intraocular pressure (A new AE with intraocular pressure > 24 mmHg and no response to treatment, except for transient intraocular pressure increase within 1 hour after intravitreal injection of study drug; AE with intraocular pressure ⩾35 mmHg and requiring treatment at any time.
  - Retinal detachment/tear
  - Retinal artery occlusion
  - Iatrogenic traumatic cataract
  - retinal pigment epithelial detachment
- Systemic AESI
  - Thromboembolic events (e.g., venous thromboembolism, arterial thromboembolism.)

If an adverse event of special interest (AESI) occurs, the investigator should complete a AESI report form. If the AESI meet the SAE standards, the investigator only needs to fill out the Serious Adverse Event Report Form. and the sponsor. The reporting process to the sponsor is the same as the SAE reporting process.

All AESI require the investigator to inform the sponsor immediately (within 24 hours of learning), and the process of reporting to the applicant is the same as that of SAE report.

8.2 THE METHODS AND TIMING FOR ASSESSING, RECORDING SAFETY PARAMETERS

The time for collection of adverse events is from the first dose to 28 days after the last dose, and only the adverse events that are still present or related to the drug are recorded afterwards.

Adverse events should be recorded on the adverse events page of the CRF, accompanied by

the following information (Including but not limited to):

- severity
- site (non-ocular, left eye, right eye, both eyes)
- its relationship to the study drug (s) or the ocular injection
- its duration (start and end dates or if continuing at final exam)
- whether it constitutes a serious adverse event (SAE)
- action taken (①measures taken for the study drug: discontinue medication, suspend medication, reduce dosage, increase dosage, no measures taken, unknown, not applicable; ②measures taken for adverse events: none, administer drug treatment, administer non-drug treatment, perform surgery, be hospitalized or otherwise (please indicate).)
- Outcome (The outcomes of AE are classified as follows: recovery, recovery with sequelae, improvement/remission, no improvement/no remission/persistence, death, and unknown.)

See the severity grades of ocular adverse event on Appendix 3 “grading scale for ocular adverse events”. The ocular adverse events not included in the grading scale will be graded according to the severity grades of systemic adverse event. See Appendix 2 for the severity grading criteria of systemic adverse events, which are divided into three grades: mild, moderate and severe.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 7.4.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated in the form of Investigator Notifications during Investigator's Brochure update. This information will be included in the subject informed consent form and should be discussed with the subject during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient’s personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator’s source documents and eCRF, however, if the AE meets the criteria of an SAE, it must be reported to the sponsor immediately.

8.3 JUDGMENT ON CORRELATION OF ADVERSE EVENTS

According to the following 5 criteria, the causal relationship of adverse events can be judged as definitely related, probably related, possibly related, possibly unrelated and unrelated. Judgment basis：

1) Definitely related:

There is a reasonable time association between adverse events and drug use; it cannot be explained by its own disease or other drugs; the exact positive withdrawal reaction; the adverse events are consistent with the pharmacological properties of the drug; if necessary, re-use the positive reaction.

2) Probably related:

If ≥3 of the following items are met, the adverse event is considered probable: a) a reasonable medication time sequence. b) It cannot be reasonably explained with the subject's known clinical symptoms and signs, environmental or toxic factors, or other treatments received by the subject. c) Adverse events disappear or alleviate after drug withdrawal or dose reduction d) Conform to the known toxicity of the suspected drug. e) Adverse events reappeared after repeated medication.

3) Possibly related:

This category applies to those whose relationship with the test drug is uncertain and cannot be excluded with certainty. If it meets the next Statement >2 items, adverse events are considered possible: a) Reasonable medication time sequence. b) It may be caused by the subject's disease, environmental or toxicity factors or other treatments received by the subject. c) Conforms to the known toxicity of the suspected drug.

4) Possibly unrelated:

Usually this type of adverse event meets 2 or more of the following criteria: a) Unreasonable medication time sequence. b) Obviously caused by the subject's disease, environmental or toxicity factors or the subject receiving other treatments. c) Does not meet the known toxicity of the suspected drug. d) Adverse events did not reappear or worsen when re-administered.

5) **Unrelated:**

Applicable to those adverse events that are obviously caused by other factors (disease, environment, etc.). And it does not meet the standards that may be irrelevant, possibly related, likely related or definitely related.

8.4 PROCEDURES FOR SERIOUS ADVERSE EVENT REPORTING

Responsibilities of Investigator

The investigator should provide timely and reasonable medical treatment for any serious adverse event occurred in the trial, whether or not related to the study drug, complete, sign and date the Serious Adverse Event (SAE) Report Form within 24 hours after being informed, and immediately report the event to the sponsor (or CRO designated by the sponsor) by email. For SAE, the description of symptoms, severity, occurrence time, treatment time, measures taken, time and method of follow-up and outcome should be recorded in detail.

The contact number and email address of the sponsor ZHAOKE to receive the serious adverse event (SAE) report is 020-28090052, and the Email address:zhyk.clinicalsafety@zhkoph.com.

If significant follow-up information is obtained after submission of the initial SAE report form, the investigator must also complete a follow-up (or summary) SAE form and report it to the sponsor. If death occurs, the investigator should provide the sponsor and the Ethics Committee with other required data, such as autopsy report and final medical report, and record detailed description of death case in the SAE Report Form.

The investigator should report suspected and unexpected serious adverse reactions provided by the sponsor to the Ethics Committee.

After receiving the relevant safety information of the clinical trial provided by the sponsor, the investigator should read and sign for it in time, consider whether the treatment of the subject should be adjusted accordingly, and communicate with the subject as soon as possible if necessary. The investigator should report the suspicious and unexpected serious adverse reactions provided by the sponsor to the Ethics Committee.

Sponsor Responsibilities

After receiving safety-related information from any source, the sponsor should immediately analyze and evaluate it, including severity, correlation with the study drug and whether it is an

expected event. The sponsor should expedite the reporting of suspected and unexpected serious adverse reactions to all investigators participating in clinical trials, clinical trial sites and ethics committees; the sponsor should report suspected and unexpected serious adverse reactions to drug regulatory authorities and health care committee, and submit an annual development safety update report.

8.5 OVERDOSE

overdose is defined as a dose that exceeds the dose specified in the study protocol or shorter dosing interval than specified in the protocol. For example, in this study, if the volume of study drug administered exceeds 50 uL, it is an overdose. If the interval between two doses of the investigational drug is less than 14 days, it is considered a drug overdose.

Cases of accidental overdose have been reported in clinical trial and post-marketing data for Lucentis®. The adverse events most frequently associated with these reported cases were intraocular pressure increased and eye pain. In the event of an overdose, intraocular pressure should be monitored and treated (at the discretion of the investigator).

In the event of accidental or intentional overdose of a study drug, even if no adverse reaction occurs, the sponsor should be informed immediately (within 24 hours of awareness), and the appropriate CRF and Overdose Form should be completed and reported according to the same procedures as SAE reporting.

Overdose will be collected from the first dose until the last dose.

8.6 PREGNANCY REPORTING

Pregnancy means that a female subject or a female partner of male subject becomes pregnant during the course of this study. If the female partner of a male subject is pregnant, the written informed consent of the female partner must be obtained before collecting any data related to pregnancy. If a pregnancy occurs, study treatment (for female subjects) should be discontinued and record in eCRF, even if SAE criteria are not met. At the same time, the investigator should complete the Pregnancy Report Form and inform the sponsor immediately (within 24 hours of awareness). The reporting process to the sponsor is the same as the SAE reporting process. If the subject decides to continue the pregnancy,the pregnancy events should be followed up once every 3 month until 1 month after the end of pregnancy to follow the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or neonatal complications.

If the outcome of the pregnancy meets the criteria for SAEs, the investigatorr should report it in accordance with the reporting procedures for SAEs. Within 24 hours of being informed, fill out the "Serious Adverse Event Reporting Form" and make a rapid report to the sponsor. The reporting process is consistent with the SAE reporting process.

The pregnancy outcomes as SAEs are as follows:

Spontaneous abortion, ectopic pregnancy, stillbirth, and congenital malformations in newborns;

All neonatal deaths that occur within one month of birth, regardless of the cause of death, be reported as serious adverse events. ,

Any infant death after one month of birth, if the researcher believes that the death may be related to the investigational drug, should also be reported as a serious adverse event.

8.7 THE TYPE AND DURATION OF THE FOLLOW-UP AFTER ADVERSE EVENTS

Once an adverse event occurred during the first dose to 28 days after the last dose, it should be

followed until the event recovers or returns to baseline or stabilizes or dies or is lost to follow-up, and should be assessed at each visit (or more frequently if necessary) for any changes in severity, relationship to study treatment, and interventions required.

Adverse events that occurred 28 days after the last dose and the investigator suspected to be related to the study treatment drug should also be followed up and evaluated as described above.

9 STATISTICAL ANALYSIS

9.1 SAMPLE SIZE DETERMINATION

This study aimed to confirm that TAB014 is non inferior to ranibizumab (Lucentis®). The main efficacy endpoint is the change in BCVA between the two groups at week 52 compared to baseline.

According to the results of three trials (ANCHOR study, MARINA study, PIER study) combined with fixed-effect meta-analysis[25], it can be known that ranibizumab compared with placebo improved BCVA by an average of 17.8 words (95 % CI is 15.95, 19.65). According to the NMPA guidance "Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry"[27], it is assumed that the difference in efficacy between the active control and placebo is represented by M1, and the non-inferiority threshold M2 is usually set as (1-f) M1. Since the main evaluation index is a high-quality index, M1 is the lower limit of 95% CI, which is 15.95. The objective of this non-inferiority trial is to prove that TAB014 retains a considerable part of the efficacy of ranibizumab. At the same time, considering the variability of previous evidence and the question of constant assumptions, if is set conservatively to 70%, which represents the maximum acceptable non-inferiority level is (1-70%) M1, that is, 30% of 15.95=4.785, and 4.5 characters are taken as the non-inferiority threshold. In addition, the literature also conducted a meta-analysis of 8 countries, multi-center, random, blind, bevacizumab and ranibizumab-controlled studies for the treatment of nAMD (more than 3000 patients receiving bevacizumab and ranibizumab), all subjects were injected with bevacizumab or ranibizumab every four weeks, and visual acuity assessment was performed a year later (average 9 injections). The non-inferiority margins

selected in the 5 studies [25] with larger sample sizes among these 8 studies were distributed in

(-3.5, -5.0). In addition, from the clinical judgment, the smallest clinical significant improvement of BCVA in nAMD disease is usually considered to be an increase of at least 10 letters [32], improvement of more than 5 words is considered clinical significant[33] in BCVA. Therefore, -4.5 was finally selected as the non-inferiority margin of this study, which is acceptable and relatively conservative from statistical analysis and clinical judgment, and also is consistent with the selection of the non-inferiority margins of previous clinical trials.

Assuming that the standard deviation of the number of letters that improves BCVA from baseline after 1 year of treatment with ranibizumab (Lucentis®) is 14.0, and the standard deviation of the number of letters that improves BCVA from baseline after 1 year of TAB014 treatment is 15.0, non-inferiority margin is -4.5, and the significance level alpha is one-sided 0.025. To have at least 80% power, the TAB014 group and the ranibizumab (Lucentis®) group are designed in a 1:1 ratio, considering a 10% drop-out rate, this study will eventually enroll244 subjects into the TAB014 group and 244 subjects into the ranibizumab (Lucentis®) group. There are 488 subjects in the two groups in total

9.2 ANALYSIS SET

Random enrollment population set (RAND): Includes all subjects who received randomization. RAND was used to describe the demographic data and baseline characteristics of the subjects. The analysis based on RAND will classify the subjects according to the treatment groups randomly assigned to them.

Full analysis set (FAS): Including all subjects who were randomly grouped and had used the investigational drug at least once and efficacy results. Subjects will be analyzed according to randomized treatment groups.

Per Protocol Set (PPS): Includes all subjects in the FAS who completed the first 3 doses, received ≥9 doses in total during the study, completed the protocol-specified assessment of the primary efficacy endpoint at week 52, and did not have a major protocol violation affecting the primary efficacy endpoint.

The FAS set and PPS set will be used for statistical analysis of the primary efficacy endpoints. Since this is a non-inferiority study, the FAS set and the PPS set will be of equal importance. If the analysis results are inconsistent, the reasons for the inconsistency should be analyzed and reasonably explained.

Safety Analysis Set (SS): All subjects who have received at least one dose of either study drug and have a documented post-baseline safety assessment. The SS set will be used for safety analysis, and subjects will be analyzed according to the actual treatment group received.

Immunogenicity analysis set: includes all subjects who received at least one dose of either study drug and at least one post-baseline immunogenicity assessment.

9.3 STATISTICAL ANALYSIS METHOD

Statistical analysis will be performed by using SAS version 9.4 or a later. Generally, descriptive statistics including the number of cases, mean, median, standard deviation, maximum and minimum values will be used to summarize continuous variables; and the number of subjects in each category and the percentage for categorical variables.

The statistical analysis method will be described in detail in the statistical analysis plan (SAP). If there is a deviation from the planned statistical analysis method in the actual analysis process, all the deviations from the statistical method and their reasons and impact on the trial conclusions will be fully explained in the final clinical trial summary report.

9.3.1 Subject disposition

The number and proportion of subjects who were screened, randomized, received at least one study drug, completed the trial, discontinued from the trial and the reason and proportion for

discontinuations will be summarized by treatment groups. Summarize the number and proportion of subjects in each analysis set, and list the reasons why subjects are excluded from the analysis set.

9.3.2 Demographics and baseline characteristics

Descriptive statistics will be used to summarize the subject's demographic data and main baseline characteristics (including the baseline value of the main efficacy) by treatment groups.

All medical history and current disease conditions will be coded using MedDRA(V25.0 or above) dictionary. The ocular (study eye and non-study eye) and non-ocular medical history and current diseases of in each group will be summarized by system organ class (SOC) and preferred term (PT), the number and proportion of subjects will be counted.

For other baseline data, descriptive statistics will be used as appropriate to summarize or list only.

9.3.3 Efficacy analysis

9.3.3.1 Primary efficacy indicator analysis

The primary efficacy indicator of this study is the change in BCVA at week 52 compared to baseline after 13 intravitreal injections of TAB014/Ranibizumab (Lucentis®).

The non-inferiority hypothesis based on the primary efficacy endpoint is

Null hypothesis H0: $\mu_{TAB014} - \mu_{Ranibizumab} \leq -4.5$.

vs.

Alternative hypothesis H1： $\mu_{TAB014} - \mu_{Ranibizumab} > -4.5$.

μ_{TAB014} and $\mu_{ranibizumab}$ represent the change of BCVA from baseline at week 52 after 13 intravitreal injections of TAB014 and ranibizumab (Lucentis®).

Descriptive statistics will be used to summarize the changes in BCVA of study eyes from baseline at 52 weeks of treatment by treatment group. Analysis of covariance model (ANCOVA) will be used for analysis, the change in BCVA of the study eye from the baseline will be used as the dependent variable, the treatment group and stratification factors (the independent reading center judges whether it is PCV) will be the independent variable, and the baseline BCVA of the study eye will be the covariate in the model. In this analysis, the missing post-baseline BCVA value will be carried forward using the LOCF method. Report the least squares mean and standard error of the BCVA change from the baseline in each group, as well as the difference between the two groups (TAB014-ranibizumab), standard error, and 95% two-sided confidence interval (CI). If the lower limit of the 95% two-sided confidence interval of the difference between the two groups is greater than -4.5, the null hypothesis will be rejected, confirming that TAB014 is not inferior to ranibizumab (Lucentis®).As a sensitivity analysis, the missing data will not be imputed, and the same ANCOVA model above will be repeated to analyze the actual observed BCVA change from the baseline at week 52.

In addition, sensitivity analysis will be performed using a repeated measure mixed effects model (MMRM). The change from baseline in BCVA of each planned post-baseline visit will be used as the dependent variable, the interaction between treatment group, visit, PCV, treatment group and visit will be the independent variable, BCVA baseline value as a covariate, and within-subject variance-covariance structure will be unstructured variance structure (UN) in the model. The missing baseline BCVA value will be not carried forward. Report the least squares mean and standard error of the change from baseline in each treatment group, as well as the difference between the two groups (TAB014-ranibizumab), standard error, and 95% two-sided CI. If the model will not be converged with the covariance structure as UN, the covariance structure as CS will be selected for the final model.

The above analysis will be repeated based on the PPS set for the indicatior efficacy endpoint.

9.3.3.2 Analysis of secondary efficacy indicators

The continuous secondary efficacy indicators will be analyzed using the same method as the primary efficacy indicatos: use ANCOVA models to analyze separately, report the least squares mean, standard error of each treatment group relative to the change from baseline, and the difference between the two groups (TAB014-ranibizumab), standard error, 95% two-sided CI and corresponding P value. The missing secondary efficacy indicators will not be imputed.

Continuous secondary efficacy indicators include:

- Compared with the baseline, the change in BCVA of the study eyes in the two groups at ;
- Compared with the baseline, through SD-OCT, the changes in the Central Subfield Thickness (CST)of the study eye in the two groups of subjects evaluated by the independent reading center at week 12, 24, 36 and week 52;
- Compared with the baseline, the fundus angiography evaluated by the independent reading center showed the change in CNV area of the study eye at week 12, 24 and week 52 .

For categorical secondary efficacy indicator, the number and proportion of subjects in each category according to each group will be reported together with the corresponding two-sided 95% exact CI (based on the Clopper-Person method), The difference in the proportion of subjects between the two groups after adjusting for stratification factor (the independent reading center

judges whether it is PCV) The Correcting stratification factor judge by the independent reading center as to whether the study eye has PCV and the Study eye's BCVA (< 24 letters or ⩾24 letters) and the 95% CI of the difference will be estimated using Mantel-Haenszel (MH) test.

The Cochran–Mantel–Haenszel (CMH) method was applied to assess treatment group differences in subject proportions after intervention, with adjustment for stratification factors including PCV status of the study eye (determined by the Independent Reading Center [IRC]) and baseline BCVA of the study eye (stratified as <24 vs. ≥24 letters). The P value for the between-group comparison was reported.

The categorical secondary efficacy indicator are as follows:

- Compared with the baseline, the proportion of subjects whose BCVA of the study eye increased >5, >10, >15,words in the two groups assessed by the independent reading center at week 12, 24 and week 52;
- Compared with baseline, compared with baseline, the proportion of subjects whose BCVA of the study eye decreased <5, <10, <15 words in the two groups assessed by the independent reading center at week 12, 24 and week 52.

9.3.4 Safety analysis

Adverse events, Serous Adverse Events, Adverse Events of special Interest, Laboratory tests (such as hematology, blood biochemistry, urinalysis), vital signs, and physical examinations are also used to assess safety. Descriptive statistics will be performed on all the safety data in the safety analysis set by treatment groups. All safety analysis will be based on the SS set.

Adverse events

Adverse events (AE) will be coded using the MedDRA(25.0 or above) dictionary.

AEs will be summarized according to ocular and non-ocular related AEs. ophthalmic -related AEs will also be further classified as AEs of study eyes and non-study eyes according to the corresponding diseased eye at the time of AE report, and summarized separately. All AEs in each treatment group, AEs related to study drugs, AEs leading to study drug discontinuation, and serious adverse events (SAEs) will be summarized and analyzed according to the MedDRA(25.0 or above) SOC and PT categories, the number and percentage of subjects with at least once for the corresponding category of AE will be calculated and reported. If the same subject has multiple AEs within the same SOC or PT, the subject will only be counted once at the corresponding SOC or PT level. The severity of AE and SAE leading to drug interruption was analyzed.

Ophthalmic examination

The safety data related to eye examinations will be summarized and described according to the study eyes and non-study eyes.

vital signs, and physical examinations

Descriptive statistics will be used to summarize the vital signs of each visit and its changes from baseline by treatment groups. The number and proportion of subjects with clinically significant abnormal values in vital signs after treatment in each treatment group will be tabulated. A listing of vital signs will be provided and the values outside the normal range will be marked in the listing.

Other safety examination

If the data is applicable, use the shift table to describe the changes in the normal/abnormal results before and after treatment of other safety examination such as laboratory tests.

9.3.5 Immunogenicity analysis

Immunogenicity is defined as that the baseline ADA is negative and the result of ADA is positive after treatment, or the baseline ADA is positive, and the titration of samples with positive ADA

after treatment is at least 4 times higher than that of baseline.

The blood sampling time points are the week 0, 12, 24, before the injection and after injection in the final visit. The blood sampling will be collected within 2 hours prior to each administration during the treatment period is. For the final visit, sampling is performed 28(± 7)days after the last dose. Summarize the number and percentage of ADA/Nab-positive subjects at each visit), Percentage of positive samples.

10 RISK MANAGEMENT PLAN

In order to better protect the safety and interests of subjects, ensure that the study protocol is strictly followed, and ensure the quality of the trial data, we will formulate a detailed risk management plan (hereinafter referred to as the plan) with all levels taken into account including safety, emergency handling, subject management, protocol operation, study medicinal product management, data management, and statistical analysis. Possible risks in the trial should be managed according to the plan, and the plan should be updated and reviewed regularly to ensure that the plan is effectively implemented during the study. The risk management plan will be kept as a separate document

11 DATA REVIEW AND DATABASE MANAGEMENT

11.1 SITE MONITORING

Before study initiation, there will be a site initiation visit or investigator’s meeting, the designated CRO representative will review the protocol and eCRFs with the investigators and their staff. During the study, the monitor will visit the site regularly to check completeness and accuracy of subjects' records, adherence to the protocol and the Good Clinical Practice regulations (GCP), study progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The investigator should maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subjects' file. The investigator should also keep the original informed consent form signed by the patient (two copies of informed consent form, one for site and one for subject).

The investigator must give the monitor access to relevant source documents (e.g. informed consent form). Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan, and site data verification (SDV). No information in source documents about the identity of the patients will be disclosed.

11.2 DATA COLLECTION

Designated investigator staff will enter the data required by the protocol into the EDC system. Automatic validation procedures within the system check for data discrepancies during and after data entry, and by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate, answering data queries timely or confirming data based on queries.

11.3 DATABASE MANAGEMENT AND QUALITY CONTROL

The design of eCRF will be implemented by an independent CRO application commercial electronic data acquisition (EDC) system designated by the sponsor, to ensure authenticity, integrity, confidentiality and traceability. Data entry will be the responsibility of the investigator or professional staff designated by the investigator, ensuring consistency with the source data. After data entry, any modifications or corrections to eCRF will be automatically recorded in the EDC. The data manager and sponsor representative can query any discrepancies or intercurrent logic issues in the eCRF, to which the investigator and (or) study representatives need to respond until all queries are resolved.

Working on behalf of the sponsor, CRO review the data entered into the eCRFs by investigator for completeness and accuracy, and to instruct investigator to make any required corrections or additions. Queries are sent to the study site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data, when necessary.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA25.0 or above) terminology.

The CF, ICGA, FFA, and OCT images of the study eye will be sent electronically to a designated, and images will be read by the independent central reading center. Data reconciliation (patient number, visit date) between the Reading Center and the clinical database will be performed for site data verification by the DM. Medical monitor will review all efficacy, safety data.

when this study is complete, protocol deviations will be confirmed. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unmasked and made available for data analysis.

11.4 DATABASE LOCK

This is a randomized double blind (patient and evaluator blinded, investigator knowledgeable) study. Data will be collected up to study completion, and the database will be locked by the data manager after all queries are resolved, and signed off by the sponsor chief medical officer. Should there be reason to unlock the database, application needs to be signed off by the sponsor chief medical officer.

11.5 APPROVAL BY THE DRUG REGULATORY AUTHORITY AND ETHICS COMMITTEE

This clinical trial has obtained clinical trial approval (approval number: 2017L04523) from the National Medical Products Administration, and can be initiated only after discussion and written approval by the Ethics Committee.

Before the start of the trial, the sponsor should provide the clinical trial approval of the National Medical Products Administration, clinical trial protocol, informed consent form and other materials to the leading site of the clinical trial and the ethics committees of all sites participating in the trial. The leading site’s Ethics Committee is responsible for reviewing the scientific and ethical rationality of the trial protocol, and the Ethics Committee of each site is responsible for reviewing the feasibility of the trial in the institution, including the qualifications and experience of the institution’s investigators, whether they have sufficient time to participate in the clinical trial, staffing and equipment conditions.

11.6 ETHICAL REQUIREMENTS FOR THE STUDY

This study will give the highest respect to subjects in accordance with the ethical principles of the Declaration of Helsinki and ICH-GCP guidelines, and each investigator will carry out the study

in accordance with applicable regulatory requirements. The principal investigator or investigator of the clinical trial should explain to the subjects the objectives of the trial and all potential possibilities. Patients who are voluntary to participate in the clinical trial and sign the informed consent form can become subjects.

11.7 INFORMED CONSENT PROCEDURES

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. Any changes to the proposed consent form must be approved by the IRB/IEC.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.8 PROTOCOL DEVIATION

The investigator should follow the protocol to perform trial-related operations to avoid protocol deviations. Protocol deviations will be judged by the sponsor and the CRO's medical monitors.

If the investigator believes that a protocol deviation is beneficial to the conduct of the study, it will be fed back to the sponsor. The sponsor will decide whether to make amendment. The amendment can be implemented only after the ethical approval is obtained. All major protocol deviations will be recorded in the Clinical study report (CSR).

11.9 PROTOCOL AMENDMENTS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, and Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol.

11.10 SUBJECT PRIVACY PROTECTION

The investigator must protect the privacy (anonymity) of subjects participating in the clinical trial. In all documents submitted to BIODLINK and ZHAOKE(Guangzhou) Ophthalmology Pharmaceutical Co., Ltd. or their representatives, only the clinical trial subject number can be used to represent the identity of the clinical trial subject, and the subject’s name, inpatient number and ID number cannot appear. The investigator must properly keep a record of the subjects’ enrollment and identification code lists with the names and addresses of clinical trial subjects.

11.11 RESPONSIBILITIES OF THE INVESTIGATOR

The investigator and personnel authorized to participate in the study should conduct the clinical trial in accordance with this clinical trial protocol, ICH Good Clinical Practice and all applicable regulatory requirements.

The investigator must follow all procedures of the clinical trial protocol and all research steps (including safety rules) provided by the sponsor. The investigator agrees to provide reliable data and all information (with the help of eCRF or other suitable tools) required by the

clinical trial protocol in an accurate and clear manner as required, and to ensure that the sponsor representatives can directly check the source documents.

If any link involves data transmission, special attention should be paid to the confidentiality of the transferred subject data. According to the clinical trial protocol, the investigator can assign persons he/she considers suitable as assistant investigators to assist in the implementation of the clinical trial. All assistant investigators should be assigned in a timely manner and a list should be made. These assistant investigators should be supervised by the investigator and bear the responsibility of the investigator. The investigator can provide them with a copy of the clinical trial protocol and all necessary information.

11.12 SPONSOR'S RESPONSIBILITIES

Clinical research associate (CRA) appointed by ZHAOKE(Guangzhou) Ophthalmology Pharmaceutical Co., Ltd. or the CRO company will contact the investigator and regularly visit the study site for clinical monitoring. The investigator should allow the CRA to access the various records of the trial (ie, eCRF, original data and any related data) according to the requirements of the CRA. The CRA should ensure the confidentiality of subjects' personal privacy. Throughout the clinical trial process, the CRA should regularly review the eCRF to confirm protocol compliance, consistency, and accuracy of the filled data. The CRA must have access to the records of all subjects whose eCRF is confirmed to have been filled in correctly. The investigator (or designees) agrees to cooperate with the CRA and ensure that the problems found during the monitoring process are resolved.

The sponsor of the clinical trial is liable to the health authorities, and will take all reasonable measures to ensure that the implementation of the clinical trial protocol meets ethical requirements, follows the clinical trial protocol, and ensure the integrity and authenticity of the data recorded on the eCRF. Therefore, the main responsibility of the monitoring team is to assist investigators and the sponsor to maintain a high level of ethical, scientific, technological, and management quality in all aspects of the clinical trial.

During the clinical research period, the CRA will regularly contact the study site through monitoring visits, letters, and telephone, verify the research progress and the compliance of the investigator and the subject with the clinical trial protocol, and handle emergencies. Monitoring visits include, but are not limited to, the following aspects: informed consent of subjects, subject recruitment and follow-up, recording and reporting of serious adverse events, recording and reporting of adverse events that require scheduled monitoring, adverse event records, distribution of study drugs, subjects' compliance with the study drug's dosing regimen, counting of the study drug, concomitant treatment, and the quality of the data.

11.13 PUBLICATION OF STUDY PROTOCOL AND RESULTS

BIODLINK and ZHAOKE(Guangzhou) Ophthalmology Pharmaceutical Co., Ltd.. will ensure that the key elements of this protocol will be posted on the China CDE clinical trials web site. On study completion and finalization of the study report, the data will be submitted for publication or posted on a publicly accessible database of clinical trial results.

11.14 FINANCIAL DISCLOSURE

Financial disclosure requires that before participating in any clinical trial activities, investigators and related study staff need to disclose any financial relationships with the sponsor or its designee. In addition, the investigator is required to update any financial relationship with the sponsor or its designee during the clinical trial and within one year after the end of the clinical trial.

11.15 CLINICAL STUDY REPORT

The final CSR will be written according to the requirements of GCP and the Structure and Content of Clinical Summary Report.

11.16 INSURANCE AND COMPENSATION

ZHAOKE(Guangzhou) Ophthalmology Pharmaceutical Co., Ltd.will purchase clinical trial liability insurance for this clinical trial in accordance with the GCP and regulatory requirements. Any part not covered thereby will be borne by ZHAOKE(Guangzhou) Ophthalmology Pharmaceutical Co., Ltd

12 APPENDIX 1 CRITERIA FOR TREATMENT DISCONTINUATION DUE TO OCULAR ADVERSE EVENTS

Event in Study Eye	Criteria for Treatment Discontinuation
Noninfectious endophthalmitis	Suspend if Noninfectious endophthalmitis is ≥ 2+ (anterior chamber cells >10 cells per mm^2) in the study eye).
Intraocular pressure	Suspend if intraocular pressure in the study eye is ≥ 30 mmHg. Treatment can be resumed when the pressure drops to < 30 mmHg, either spontaneously or by treatment, as determined by the Investigator.
Vitreous hemorrhage	Suspend if there is vitreous hemorrhage sufficient to produce a ≥ 30-letter decrease in visual acuity in the study eye compared with the last assessment of visual acuity prior to the onset of the vitreous hemorrhage. Treatment will be permitted when the vitreous hemorrhage improves to allow a visual acuity score improvement to a < 30-letter decrease.
Sensory rhegmatogenous retinal hole or detachment (including macular hole)	Suspend if a new retinal hole is identified in the study eye. Ttreatment should be suspended. ≥23 days after the retinal hole has been properly treated, the investigator will determine whether the study and administration can continue. If the study eye develops stage 3 or 4 macular holes or rhegmatogenous retinal detachment, treatment must be terminated
Local infection	Suspend if there is: infectious conjunctivitis, infectious keratitis, infectious scleritis or endophthalmitis in either eye.
VA decrease	Suspend the treatment if BCVA decrease of ≥30 letters (Compared with baseline VA values) related to treatment.

The ophthalmologist may discontinue a patient from additional treatment for other safety reasons if in the best medical judgment of the treating ophthalmologist it is believed that there is no chance of any benefit to the patient from additional intravitreal injections in terms of preserving vision or retinal anatomy.

13 APPENDIX 2 SEVERITY GRADES FOR SYSTEMIC ADVERSE EVENTS

Severity	Criteria
mild	Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
moderate	Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
severe	Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating .

NIA Adverse events and Serious adverse event Guidelines 2018/9

14 APPENDIX 3 STAGING SCALE FOR OCULAR ADVERSE EVENTS

Stages	Standards
Ocular Inflammation: defined as active inflammatory cell in aqua oculi and/or in vitreous, or visible persistent fluid in anterior chamber (do not include the pigment cell or obvious subsided old inflammation) (Refer to the Appendix VI)	
severe	Any 4+ ocular inflammations or 2-3+ ocular inflammations, which are not decrease to 1+ or lower within 30 days.
moderate	Any 2+ ocular inflammations do not decrease to 1+ or lower within 14 days, or any 3+ ocular inflammation decrease to 1+ or lower within 30 days.
mild	Any 2+ ocular inflammation decrease to 1+ or lower within 14 days.
VA Decrease: (Compared with the VA measured before injection)	
severe	VA decrease of ≥30 letters within 14 days post-injection of TAB014/ranibizumab.
moderate	VA decrease of 21 to 29 letters within 14 days post-injection of TAB014/ranibizumab; or VA decrease of 15 to 20 letters within 14 days post-injection of TAB014/ranibizumab and do not improve until the next injection.
mild	VA decrease of 15 to 20 letters within 14 days post-injection of TAB014/ranibizumab and it improved until the next injection.
IOP: (Compared with the IOP measured before injection)	
severe	Light perception persistent loss of >15 minutes due to IOP increase, or, IOP increase or decrease of >20mmHg over 14 days.
moderate	IOP increase or decrease of >20mmHg within 24 hours post-injection of TAB014/ranibizumab, or IOP increase or decrease of >10-20mmHg over 14 days.
mild	IOP increase or decrease of 10-20 mmHg within 24 hours post-injection of TAB014/ranibizumab, and it relieved or eliminated within 14 days.
Vitreous Hemorrhage (Refer to the Appendix VII)	
severe	Vitreous Hemorrhage ≥2+ and eliminate without 14 days.
moderate	Vitreous Hemorrhage ≥2+ and eliminate within 14 days.
mild	Trace or Vitreous Hemorrhage 1+.
Retinal tear or detachment:	

severe	Tear or detachment of the retina involving the macular during the study.
moderate	Tear or detachment of the retina not involving the macular during the study.
mild	None retinal tear or detachment.
Retinal Hemorrhage:	
severe	The area of new retinal hemorrhage >1 disc area involving the center of the fovea, or the increase of the area of the original retinal hemorrhage >1 disc area involving the center of the fovea.
moderate	The area of new retinal hemorrhage >1 disc area not involving the center of the fovea, or the increase of the area of the original retinal hemorrhage >1 disc area not involving the center of the fovea.
mild	The area of new retinal hemorrhage ≤1 disc area, or the increase of the area of the original retinal hemorrhage ≤1 disc area.

15 APPENDIX 4 GRADING SCALES FOR OCULAR INFLAMMATION*

Flare	
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slit-lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein detectable in the anterior chamber. This protein is visible only with careful scrutiny by an experienced observer using slit-lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Mild amount of protein detectable in the anterior chamber. The presence of protein in the anterior chamber is immediately apparent to an experienced observer using slit-lamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2-3+	Moderate amount of protein detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+.
4+	A large (severe) amount of protein is detectable in the anterior chamber. Similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It needs to be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood–aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (e.g., 1+ flare with fibrin).
Cells	
0	No cells are seen in any optical section when a large slit-lamp beam is swept across the anterior chamber.
Trace	Rare (1–5) cells are observed when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	6–15 cells/optical section are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
2+	16–25 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.

3+	26–50 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

This is a modification of the grading system described by Hogan MH, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47:155-70

16 APPENDIX 5 GRADING SCALE FOR VITREOUS HEMORRHAGE DEGREE

Grading Scale for Vitreous Hemorrhage		
Grade	Description	
0(None)	Retinal visible	
Trace	Retina is visible, red corpuscle is visible	
1+	The details of the retina is visible and some hemorrhage concomitant	
2+	The big retina is visible, but the detailed structure of the central retina is not visible	
3+	Retinal red reflex is visible, but sub-ambitus central retinal structure is not visible	
4+	Retinal red reflex does not exist	
Grading Scale for Vitreous Cells*+		
Cells in Retroilluminated Field	Description	Grade
0-1	Clear	0
2-20	Few opacities	Trace
21-50	Scattered opacities	1
51-100	Moderate opacities	2
101-250	Many opacities	3
>251	Dense opacities	4

This is a modification of the grading system described by Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. 2nd rev.ed. New York, New York: Mosby, 1996:64.

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A Multicenter, Randomized, Double-blind Phase III Clinical Study Evaluating the Efficacy and Safety of TAB014 Versus Ranibizumab (Lucentis®) in Patients with Neovascular Age-Related Macular Degeneration

Statistical Analysis Plan

Statistical Analysis Plan Version:	**V1.0**
Statistical Analysis Plan Version Date:	**7 Aug., 2023**
Protocol No.:	**TOT-CR-TAB014-III-01**
Protocol Version:	**V1.3**
Protocol Version Date:	**8 Dec., 2022**
Sponsor:	**ZhaoKe (Guangzhou) Ophthalmology Pharmaceutical Co., Ltd.**
CRO	**Tianjin Happy Life Technology Co., Ltd.**

Signature Page

Your signature on this page will indicate that you confirm that you agree to the statistical analysis of this trial in accordance with this plan.

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Document Revision History

Version Number	Date	Author/Updater	Comments
1.0	12 Dec., 2022	Wang Yu	Creator
1.0	7 Aug., 2023	Wang Yu	Revised and finalized based on feedback from all parties

Contents

Abbreviations

Abbreviations	Full Name
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CRF	Case Report Form
CNV	Choroidal Neovascularization
CF	Color Fundus
CST	Central Subfield Thickness
eCRF	Electronic Medical Record Report Form
FAS	Full Analysis Set
FFA	Fluorescein Fundus Angiography
GLOBALB3Mar22_CHS	Coded Dictionary of Concomitant Medication
ICGA	Indocyanine Green Angiography
IOP	Intraocular Pressure
LOCF	Last Observation Carried Forward
nAMD	Neovascular Age-related Macular Degeneration
Nab	Neutralizing Antibody
NA	Not Applicable
MedDRA	Medical Dictionary for Regulatory Activities
OCT	Optical Coherence Tomography
PCV	Polypoidal Choroidal Vasculopathy
PPS	Per Protocol Set
PT	Preferred Terms
Q1	First Quartile
Q3	Third Quartile
VA	Corrected Vision
VEGF	Vascular Endothelial Growth Factor
RAND	Randomized Population Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Safety Set
TFL	Tables, Forms, Lists

1. Introduction

This statistical analysis plan primarily delineates the statistical analysis procedures for this study, supplementing and refining the statistical analysis methods, data processing principles, and results presentation approaches outlined in the study protocol. This statistical analysis plan is based on the following documents:

Documents	Date	Version
Protocol	8 Dec., 2022	V1.3
eCRF	16 Feb, 2023	V5.0

2. Study Overview

2.1 Study objectives, endpoints, estimated goals

2.1.1 Study objectives and endpoints

Objectives	Endpoints
Primary objective	
To compare the efficacy of TAB014 and Ranibizumab (Lucentis®) in patients with neovascular age-related macular degeneration.	Primary efficacy endpoints: • Change from baseline in BCVA at week 52 of the study eye in both groups of subjects. Secondary efficacy endpoints: • Changes from baseline in BCVA at weeks 12, 24, and 36 in the study eye for both groups of subjects; • Proportion of subjects in both groups whose BCVA improved by >5, >10, and >15 letters in the study eye at weeks 12, 24, and 52 compared with baseline; • Proportion of subjects in both groups whose BCVA decreased by <5, <10, and <15 letters in the study eye at weeks 12, 24, and 52 compared to baseline; • Change from baseline in central subfield thickness (CST) in study eyes at weeks 12, 24, 36, and 52 in both groups of subjects as assessed by an independent film reading center using SD-OCT; • Changes from baseline in choroidal neovascularization (CNV) area in the study eye at weeks 12, 24, and 52, as assessed by an independent film reading center using fundus photography;
Secondary objective	
To compare the safety of TAB014 and Ranibizumab (Lucentis®) in patients with neovascular age-related macular degeneration.	• Vital signs • Physical examination • ECG • Laboratory tests • Ophthalmic examination

Objectives	Endpoints
	• Ocular and non-ocular adverse events and serious adverse events • Adverse Events of Special Interest (AESI)
To evaluate the immunogenicity of TAB014 in patients with neovascular age-related macular degeneration.	• Number and percentage of ADA/Nab positive subjects at week 0, week 12, week 24 pre-dose and final visit, and percentage of positive samples.

2.1.2 Estimated goals

The primary clinical question of interest is the difference in change in best-corrected visual acuity (BCVA) at week 52 from baseline in the study eye following intravitreal administration of TAB014 (recombinant humanized anti-VEGF monoclonal antibody injection) versus intravitreal administration of Lucentis® (Ranibizumab injection) in all randomized patients with neovascular age-related macular degeneration.

Definition of the main estimated goals:

- Target population: Patients with neovascular age-related macular degeneration randomized in this study.
- Treatment: The study group will receive TAB014 (recombinant humanized anti-VEGF monoclonal antibody injection) via intravitreal injection at a dose of 1.25 mg per administration (i.e., 0.05 mL per administration); the control group will receive Lucentis® (Ranibizumab injection) via intravitreal injection at a dose of 0.5 mg per administration (i.e., 0.05 mL per administration).
- Objective variable: Change in BCVA from baseline in study eyes at week 52.
- Concomitant events and handling strategies:

Concomitant Events	Handling Strategy	Remarks
Termination of treatment with prohibited drugs or treatments that affect the efficacy of treatment	Hypothetical strategy Exclude post-concomitant event data without imputation	Exclude confounding factor interference and evaluate the non-inferiority between the study group and the control group
Discontinue treatment for reasons other than the use of prohibited drugs or treatments	Therapy strategy Continue collecting usage data even if concurrent events occur	
Omit study drug administration	Therapy strategy Continue collecting usage data even if	

	concurrent events occur	

- Summary at the group level: Compare the changes in BCVA of the study eyes in the study group and the control group at week 52 from baseline.

2.2 Study design

2.2.1 Overall design

This study employs a randomized, double-blind, multicenter, non-inferiority design comparing TAB014 with Ranibizumab (Lucentis®). The target population consists of patients with neovascular age-related macular degeneration (nAMD). The objective is to evaluate the efficacy, safety, and immunogenicity of TAB014 versus Ranibizumab (Lucentis®). A total of 488 subjects are planned to be included and randomized into the study group (TAB014 group) or the control group (Ranibizumab group) in a 1:1 ratio, with 244 cases in TAB014 group, and 244 in the Ranibizumab (Lucentis®) group. Randomization stratification factors include polypoidal choroidal vasculopathy (PCV) in the study eye (yes or no as judged by an independent film reading center) and baseline BCVA in the study eye (<24 letters or ≥24 letters).

This study includes the screening period, the randomization/baseline/first-dose period, the treatment period, and the final visit. The screening period lasts 28 days. Eligible subjects will be randomized to receive the first dose on the day of randomization, followed by entry into the treatment period with intravitreal injections administered every 4 weeks. The final visit will be conducted 4 weeks after the last treatment. The study group will receive TAB014 administered via intravitreal injection every 4 weeks at a dose of 1.25 mg (0.05 mL) per injection. The control group will receive Ranibizumab (Lucentis®) administered via intravitreal injection every 4 weeks at a dose of 0.5 mg (0.05 mL) per injection. The final visit is scheduled at Week 52.

Best-corrected visual acuity is assessed every 4 weeks by a blinded visual acuity evaluator.

2.2.2 Randomization and blinding

Subjects are randomized in this study using IWRS. An independent unblinded statistician generates the subject randomization list (blinding codes) and the investigational product randomization list using SAS software (version 9.4 or higher). Successful screening subjects will be randomized the study group or control group in a 1:1 ratio to receive TAB014 or Ranibizumab (Lucentis®).Randomization stratification factors include PCV of the study eye (yes or no judged by the independent film reading center) and baseline BCVA in the study eye (<24 letters or ≥24 letters). Randomized subjects will be assigned an available random number, which the investigator will record in the source file. For the randomized subjects who have withdrawn/withdrawn from the clinical trial for any reason, regardless of whether the investigational product has been administered, their assigned random number cannot be reallocated to other subjects.

This study employs a double-blind design, maintaining blinding for subjects, evaluating investigators, ophthalmic specialists (including BCVA examiners), study nurses, independent film reading center staff, and the Sponsor. Drug blinding is performed by a third-party blinding packaging company under the supervision of non-blinded statisticians to complete the blinding packaging of clinical investigational products. Packaged study drugs are provided by a double-blind pattern during the study to maintain the double-blindness of the study. Due to the inability to ensure complete uniformity in the smallest packaging of the drugs, this study will involve unblinded pharmacists, unblinded treatment nurses, unblinded injection physicians, and unblinded CRAs.

The roles of non-blinded injecting physicians and non-blinded treatment nurses will be specified in the site log. Once assigned, these roles cannot be changed in subsequent studies. To maintain subject blinding, the unblinded injection physician and unblinded nurse must ensure that the subject does not come into contact with the drug or its packaging before, during, or after treatment.

The best visual acuity examiner must not have access to any prior visual acuity test results for any subject.

To meet the blindness requirements of the study, the work content and blindness of the participants are as follows:

Personnel	Blinding	Work during the Study Period
Specialist ophthalmic examiners (including BCVA examiners)	Maintain blindness to grouping	Undergo vision and other eye examinations Report the assessed visual acuity to the investigator
Study nurse	Maintain blindness to grouping	Assist the investigator in the care of the subject
Independent film reading center staff	Maintain blindness to grouping	Conduct OCT, CF, FFA and ICGA film reading and provide reports
Investigator responsible for assessment	Maintain blindness to grouping	Receive vision test results Perform and manage all assessments (intraocular pressure measurement, slit-lamp examination, fundus examination, OCT, CF, ICGA, and FFA examinations) Provide guidance to physicians involved in the injection
Non-blinded injection physician	No blinding for grouping	Responsible for dosing therapy
Unblinded pharmacist, unblinded treatment nurse, unblinded CRA (limited	No blinding for grouping	Assist in the preparation and give treatment, conduct drug verification and review drug inventories, etc.

number)		

2.2.3 Sample size

Assuming the standard deviation of letters in BCVA improvement from baseline after 1 year of treatment with Ranibizumab (Lucentis®) is 14.0, and the standard deviation of letters gained in BCVA from baseline after one year of TAB014 treatment is 15.0, with a non-inferiority margin of −4.5 and a one-sided alpha level of 0.025. To achieve 90% power, the TAB014 and Ranibizumab (Lucentis®) groups are designed in a 1:1 ratio, accounting for a 10% dropout rate. This study will ultimately enroll 244 subjects in the TAB014 group and 244 subjects in the Ranibizumab (Lucentis®) group, totaling 488 subjects across both groups.

3. Analysis Set Definition

Randomized population set (RAND): Includes all subjects randomized. RAND is used to describe subject demographics and baseline characteristics. The RAND-based analysis will categorize subjects according to their randomized treatment groups.

Full analysis set (FAS): Includes all subjects who have been randomized and used the investigational product at least one dose. Subjects will be analyzed according to their randomized treatment groups.

Per protocol set (PPS): Includes all subjects in the FAS who have completed the first 3 doses within the first 3 months, received ≥9 doses during the study, completed the primary efficacy endpoint assessment as specified in the protocol at Week 52, and have no major protocol deviations affecting the primary efficacy endpoint.

Safety set (SS): All subjects who have received at least one dose of the study drug and have at least one post-baseline safety assessment constitute the SS for this study. The SS set will be used for safety analysis and subjects will be analyzed according to the treatment group actually received.

Immunogenicity analysis set: All subjects who have received at least one dose of the study drug and have at least one post-baseline immunogenicity result constitute the immunogenicity analysis set for the study.

4. Data Processing

4.1 Definition of baseline values

The baseline value is defined as the last valid measurement collected prior to the first dose.

4.2 Definition of visit window

Analyze all data collected through visits using the study visits (scheduled visits only) as defined in the study flowchart and eCRF; data from unscheduled visits are presented in listings only, but the definition of baseline values should account for unscheduled data.

4.3 Missing data handling rules

4.3.1 Missing treatment of efficacy endpoints

The handling of missing data for efficacy endpoints is detailed in the statistical analysis methods for each indicator below.

4.3.2 Management of missing dates for previous/concomitant medications and previous/concomitant non-drug therapies

For missing dates regarding previous/concomitant medication use or previous/concomitant non-pharmacological treatments, unless otherwise specified, missing dates shall be imputed using the following methods prior to analysis. The imputation method for missing start/end dates of previous/concomitant non-pharmacological treatments shall be consistent with that for previous/concomitant medication use.

Missing start dates of previous/concomitant medications:

Missing Medication Start Date	Filling Method
Only days missing	Year and month match those of the first dose, with the day filled in as the day of the first dose.
	If the year falls after the year of the first dose, or if the year coincides with the year of the first dose but the month falls after the month of the first dose, the day shall be filled in as the first day of that month.
	If the year is before the year of the first dose, or the year is the same as the year of the first dose but the month is before the month of the first dose, the day shall be filled in as the first day of that month.
Month and day missing	If the year matches the year of the first dose, the month and day should be filled in as the month and day of the first dose.
	If the year falls after the year of the first dose, the month and day should be filled in as the first day of that year (January 1).
	If the year is before the year of the first dose, the month and day should be filled in as the first day of the year (January 1).
Date completely missing	The year, month, and day should be filled in as the year, month, and day of the first dose.

If the medication end date (non-fill) is earlier than the fill start date, the start date of medication should be filled in as the end date of medication.

Missing end dates of previous/concomitant medications:

Missing Medication End Date	Filling Method
Only days missing	The end date of medication should be filled in as the minimum value (among the end date of the subject's study*, the last day of the month, and the date of death *)
Month and day missing	The end date of medication should be filled in as the minimum value (among the end date of the subject's study*, December 31 of the year, and the date of death *)
Date completely missing	The end date of medication should be filled in as the minimum value of the two (the end date of the study for the subjects and the date of death)

*Replace the year or month that is not missing by date.

If the filled medication end date is earlier than the medication start date (not filled), the end date of medication should be filled in as the medication start date.

If both the start and end dates of the medication are filled, and the filled medication end date is earlier than the filled medication start date, the start date of medication should be filled in as the medication end date.

4.3.3 Handling of other missing data

Unless otherwise specified, no imputation will be performed for missing data in other categories.

When listing data, it will still be presented according to the originally collected dataset.

5. Statistical Analysis

5.1 General principles

All data are processed, summarized, and analyzed using SAS® 9.4 or later versions. Unless otherwise specified, the following principles will apply to all TFLs:

Item	Handling Method
Treatment group label and result display order	TAB014 group, Ranibizumab group, total
Table	The summary table displays data by treatment group and visit.
List	Unless otherwise specified, all data collected are presented by subject and visit.
Descriptive summary of continuous variables	Number of cases, mean, standard deviation, median, Q1, Q3, minimum and maximum.
Descriptive summary of categorical variables	Frequency and percentage [n (%)].
Percentage denominator	Unless otherwise specified, the denominator is the number of subjects in each treatment group of the analyzed population.
List "Missing" as a category	For the efficacy endpoints, "missing" is listed as a category when there is a treatment group with a number of deletions greater than zero.

Percentage	Keep one decimal place, and when the percentage is 0, the frequency and percentage will be displayed as "0" instead of 0 (0.0).
Mean, standard deviation, median	Displays 1 decimal place more than the collected value.
Standard deviation, standard error, confidence interval (CI)	Displays 2 decimal place more than the collected value.
P value	All P values will be rounded to 3 decimal places. If the P value is less than 0.001, it will be represented as "<0.001"; if the P value is greater than 0.999, it will be represented as ">0.999"
Decimal display limit	3 decimal places
Date format (list)	YYYY-MM-DD

5.2 Subject distribution and analysis data sets

Based on all screened subjects, summarize the number of subjects screened, screening successes, screening failures (including randomization failures), and the number and percentage of subjects for each screening failure reason.

Based on successfully randomized subjects, summarize the number and percentage of subjects in each treatment group who entered the randomized enrollment population, full analysis set, per protocol set, safety set, and immunogenicity analysis set.

Based on the successfully randomized subjects, summarize the number and percentage of subjects who completed the treatment in each treatment group, the main reasons for early termination of treatment, the completion of the study and the main reasons for early withdrawal from the study in the successfully randomized subjects.

Based on all screened subjects, list the screening status of subjects, including screening number, screening outcome, reason for screening failure, other reasons, randomization outcome, reason for randomization failure, and other reasons.

Based on the successfully randomized subjects, list the treatment completion and study completion status for each subject, including subject screening number/random number/group, whether treatment was completed per protocol, treatment completion/decision to discontinue treatment date, last dose date, reason for early treatment discontinuation (other please specify), protocol deviation category (other please specify), whether study was completed, study completion/early termination date, reason for early study termination (other please specify), and consent withdrawal date.

Based on the successfully randomized subjects, list the subjects' inclusion in each analysis dataset, including subject screening number/random number/group, randomized population set, full analysis set, per protocol set, safety set, and immunogenicity analysis set.

5.3 Protocol deviation

Based on all successfully randomized subjects, summarize the number and percentage of subjects

with at least one major protocol deviation and those with at least one major protocol deviation in each deviation category by treatment group.

List instances of protocol deviations in subjects, including subject screening number/random number/group, deviation category, severity, etc.

Protocol deviations must be identified prior to database lock.

5.4 Demographics and baseline characteristics

5.4.1 Demographic and other baseline endpoints

Quantitative endpoints in demographic studies include age (years), height (cm), weight (kg), tobacco consumption (cigarettes), alcohol consumption (mL), and days since nAMD diagnosis. Qualitative endpoints include gender, ethnicity, affected eye for nAMD diagnosis, study eye, study eye BCVA classification (<24/≥24), presence of polypoidal choroidal vasculopathy (PCV) in the study eye, prior anti-VEGF therapy in the study eye, allergy history, smoking history, tobacco type, tobacco use frequency, alcohol history, alcohol type, alcohol use frequency, infection screening including HBsAg, HCV-Ab, HIV-Ab, TP-Ab.

Based on the randomized population set, statistically describe the quantitative endpoints in each treatment group as continuous variables and the qualitative endpoints as categorical variables.

List the demographic characteristics of the subjects, including screening number/random number/group assignment, gender, age (years), height (cm), weight (kg), and ethnicity.

List the subject's nAMD history, including screening number/random number/group, nAMD diagnosis eye, left eye diagnosis date, right eye diagnosis date, study eye, date of last anti-VEGF treatment within one year prior to screening, whether the study eye had previous anti-VEGF treatment, and number of previous anti-VEGF treatments in the study eye within one year prior to screening.

List the subject's allergy history, including screening number/random number/group, whether there is a history of drug or food allergy, name of allergic drug or food, and allergy symptoms.

List the subject's smoking history, including screening number/random number/group, subject's smoking frequency, start date, duration, end date, tobacco type, amount of use, and frequency of use.

List the subject's drinking history, including screening number/random number/group, subject's drinking frequency, start date, duration, end date, type of drinking, amount of use, and frequency of use.

List the subject's infection screening results, including screening number/random number/group, whether testing is performed, reason if not performed, sampling date, test item, result, HBV DNA/HCV RNA result, clinical significance of HBV DNA/HCV RNA.

5.4.2 Other medical history

Code medical history using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later.

Summarize the number and percentage of subjects with other medical conditions in each treatment group based on the randomized population set by systemic organ class and preferred terms.

List the subject's other medical history, including screening number/random number/group, disease/diagnosis, disease location, start date, ongoing status, end date, and whether treatment is given during screening.

5.4.3 Previous/concomitant medication

Previous/concomitant medications should be coded using the GLOBALB3Mar22_CHS dictionary or a later version.

Previous medications and concomitant medications are defined as follows:

Previous medications refer to drugs discontinued prior to the date of the first dose.

Concomitant medication refers to medication with a start date on or after the day of the first dose, or a start date before the date of the first dose and an end date on or after the date of the first dose, or continued medication.

If it still cannot be determined as "previous medication" or "concomitant medication" by filling in the missing date, it will be regarded as concomitant medication.

Based on the randomized population set, summarize the number and percentage of subjects using previous/concomitant medication by treatment group according to treatment subgroup (ATC2) and drug preferred name (PN).

List the subject's previous and concomitant medication details, including screening number/random number/group, drug name, start date, duration, end date, single dose, dose unit (please explain for others), route of use (please explain for others), frequency of use (please explain for others), reason of use, if the reason is "AE", please mark AE number/name, if the reason is "other medical history", please mark medical history number/name.

5.4.4 Previous/concomitant non-drug therapy

Previous/concomitant non-drug therapy should code using the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 25.0 or later.

Previous non-drug therapy and concomitant non-drug therapy are defined as follows:

Previous non-drug therapy refers to non-drug therapy discontinued prior to the date of first dosing.

Concomitant non-drug therapy refers to non-drug therapy with a start date on or after the day of the first dose, or a start date before the date of the first dose and an end date on or after the date of the first dose, or continued therapy.

If it still cannot be determined as "previous non-drug therapy" or "concomitant non-drug therapy" by filling in the missing dates, it will be regarded as concomitant non-drug therapy.

Summarize the number and percentage of subjects receiving non-drug therapy in each treatment group based on the randomized population set by systemic organ class and preferred terms.

Present a detailed list of subjects' previous and concomitant non-drug therapies, including screening number/random number/group, visit name and date, non-drug therapy name, reason for therapy (if the reason is "AE", specify the AE number/name; if the reason is "other medical history", specify the medical history number/name), start date, whether ongoing, and end date.

5.5 Treatment compliance

Treatment compliance is calculated as follows: Compliance (%) = Actual number of doses in the study eye/planned number of doses in the study eye × 100%

Here, the actual number of doses administered is the sum of doses given during all visits, and the planned number of doses (times) = the count corresponding to the last dose administration visit.

Statistically describe the compliance of each treatment group based on the randomized population set according to continuous variables.

Describe and statistically analyze the treatment compliance of each treatment group at different cycles (first dose - week 12, week 13 - week 24, week 25 - week 52) based on the randomized population set, and count the number and proportion of subjects who do not receive (13 doses - actual number of doses) 1, 2, 3 or more doses at week 52.

List the treatment compliance of the subjects, including the screening number/random number/group, study eye, first dose date of the study eye, last dose date of the study eye, actual number of doses administered to the study eye, planned number of doses for the study eye, and compliance (%).

5.6 Efficacy analysis

5.6.1 Statistical analysis of the main estimated goals

5.6.1.1 Hypothesis testing

The non-inferiority hypothesis testing based on the primary efficacy endpoint is as follows:

Null hypothesis H_0: $\mu_{TAB014} - \mu_{Ranibizumab} \leq -4.5$

Alternative hypothesis H_1: $\mu_{TAB014} - \mu_{Ranibizumab} > -4.5$

Where, μ_{TAB014} and $\mu_{ranibizumab}$ represent the mean changes from baseline in BCVA at week 52 after 13 intravitreal injections of TAB014 and Ranibizumab (Lucentis®), respectively.

If the lower limit of the 95% two-sided confidence interval of the difference between the two groups is >-4.5, the null hypothesis will be rejected, confirming that TAB014 is non-inferior to ranibizumab (Lucentis®).

5.6.1.2 Main analytical methods

Analysis is based on FAS and PPS respectively.

Based on the concomitant event treatment strategy in the main estimated goals, after carrying forward the missing BCVA value after baseline using LOCF method (if applicable), the change from baseline in BCVA at Week 52 for the study eye in each treatment group is statistically described as a continuous variable. An analysis of covariance (ANCOVA) model is employed to report the least squares mean, standard error, and 95% two-sided confidence interval (CI) for the change from baseline in BCVA for each treatment group, as well as the difference in change from baseline between the two groups (TAB014 - Ranibizumab), along with the standard error and 95% two-sided CI. In the ANCOVA model, the change from baseline in BCVA for the study eye serves as the dependent variable, with treatment group and randomization stratification factor (whether the study eye had PCV) as independent variables, and the baseline BCVA value of the study eye as a covariate. Refer to SAS Code:

```
PROC MIXED;
CLASS GROUP STRATA;
MODEL CHG = GROUP BASELINE STRATA;
LSMEANS GROUP/PDIFF CL;
ESTIMATE 'T vs. C' GROUP 1 -1/CL ALPHA = 0.05;
RUN;
```

5.6.1.3 Sensitive analysis

5.6.1.3.1 Sensitivity analysis 1

Sensitivity analysis is performed based on FAS using mixed-effects models for repeated measures (MMRM). The relative change in BCVA from baseline at each post-baseline scheduled visit serves

as the dependent variable. The independent variables include treatment group, visit, PCV, and the interaction between treatment group and visit. Baseline BCVA serves as a covariate. The within-subject variance-covariance structure is set as an unstructured variance structure (UN). Missing post-baseline BCVA values are not carried forward. The least-squares mean, standard error of change from baseline for each treatment group and the difference in change from baseline between the two groups (TAB014 - Ranibizumab), standard error, and 95% two-sided CI are reported. If the model does not converge when the covariance structure is UN, the covariance structure can be chosen as CS for the final model. Refer to SAS Code:

PROC MIXED;

CLASS GROUP STRATA AVISIT RANDNO;

MODEL CHG = GROUP AVISIT BASELINE STRATA GROUP* AVISIT;

Repeated AVISIT/subject = RANDNO type = un;

LSMEANS GROUP/PDIFF CL;

RUN;

5.6.1.3.2 Sensitivity analysis 2

The BCVA values missing after baseline are not processed. The analysis is conducted based on FAS using the same method as in 5.6.1.2.

5.6.1.4 Central effect

Due to the large number of sites in this study, and all participating sites are from China, there is no expected treatment difference between them, and the central effect will not affect the clinical effect. Therefore, there is no need to consider the impact of the central effect on the primary and secondary variables, and data from all centers will be pooled for analysis.

5.6.1.5 Subgroup analysis

Based on the classification of baseline BCVA (<24/≥24) in the study eye and the presence of polypoidal choroidal vasculopathy (PCV) in the study eye, different subgroups are formed, with the primary efficacy endpoint analyzed using the same methods as in Section 5.6.1.2 based on the FAS and PPS, and forest plots prepared.

5.6.2 Analysis of secondary efficacy endpoints

➢ Continuous secondary efficacy endpoints include:

- Changes from baseline in BCVA at weeks 12, 24, and 36 in the study eye for both groups;

- Change from baseline in central subfield thickness (CST) in study eyes at weeks 12, 24, 36, and 52 in both groups of subjects as assessed by an independent film reading center using SD-OCT;

- Changes from baseline in choroidal neovascularization (CNV) area in the study eye at weeks 12, 24, and 52, as assessed by an independent film reading center using fundus photography.

➢ Secondary efficacy endpoints include:

- Proportion of subjects with an improvement in BCVA of >5, >10, and >15 letters at week 12, week 24, and week 52 in the study eye from baseline;

- Proportion of subjects whose BCVA decreased by <5, <10, and <15 letters in the study eye at weeks 12, 24, and 52 compared to baseline.

The continuous secondary efficacy endpoints should be analyzed using ANCOVA based on FAS. The least squares mean, standard error, 95% bilateral CI of the changes from baseline in each treatment group, as well as the differences in changes from baseline between the two groups (TAB014 - Ranibizumab), standard error, 95% bilateral CI and the corresponding P values should be reported. In the ANCOVA model, the change from baseline in indicators for the study eye serves as the dependent variable, with treatment group and randomization stratification factor (whether the study eye had PCV) as independent variables, and the baseline indicator value of the study eye as a covariate. For missing secondary efficacy endpoints, no imputation will be performed.

For the FAS-based secondary efficacy endpoint, the number and proportion of subjects in each category will be reported by treatment group, along with the corresponding two-sided 95% exact CI (based on the Clopper-Pearson method). The difference in subject proportions between the two groups, adjusted for stratification factors (whether the study eye has PCV; baseline BCVA of the study eye (<24 letters or ≥24 letters)), and the two-sided 95% CI for the difference will be estimated using the Mantel-Haenszel (MH) method. The Cochran–Mantel–Haenszel (CMH) method is used to compare the difference in subject proportions between treatment groups after adjusting for stratification factors (whether the study eye has PCV; baseline BCVA of the study eye (<24 letters or ≥24 letters)). The P value for the between-group comparison is reported. Refer to SAS Code:

Calculate the 95% CI based on the Clopper-Person method:

```
proc freq data = XX;
table response/binomial (exact) cl alpha = 0.05;
by group;
run;
```

Calculate 95% CI using the MH method and compare intergroup differences via the Cochran–

Mantel–Haenszel (CMH) method:

proc freq data = XX;

table pcv*bcva*group* response/cmh commonriskdiff (TEST = MH) alpha = 0.05;

weight f;

run;

5.7 Safety analysis

5.7.1 Drug exposure

Drug exposure circumstances encompass the number of drug treatments and the duration of drug exposure.

Duration of drug exposure is the time from the last dose to the first dose in the subject's study eye (including the time of temporary interruption during treatment) and is calculated in days as follows:

Number of drug treatments (times) = sum of all actual treatment times.

Duration of drug exposure (days) = date of last dosing-date of first dosing + 1.

If the first dose date is missing, the randomization date should be used as the first dose date; if the last dose date is missing, the duration of exposure cannot be calculated.

The cumulative drug exposure dose is the sum of the actual dose (mL) administered at all visits during the medication period.

Statistically describe the duration of drug exposure and cumulative drug exposure dose for each treatment group as continuous variables based on the safety set.

List the drug exposure of subjects, including screening number/random number/group, study eye, first dose date for the study eye, last dose date for the study eye, exposure duration (days), and cumulative drug exposure dose (mL).

5.7.2 Adverse Event

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 (or later), and ophthalmic adverse events will be graded according to the ophthalmic adverse event scale, and non-ophthalmic adverse events will be graded according to the NIA guidelines for adverse events and serious adverse events (September 2018). Adverse events (AEs) are assessed as related (including AEs "definitely related", "probably related", "possibly related", or with absence of relationship) or unrelated (including "likely unrelated", "not related") to the investigational product/ocular injection/protocol-required ophthalmic examination.

Treatment Emergent Adverse Event (TEAE) is defined as any adverse medical event occurring in

a subject after receiving the investigational product, which may manifest as symptoms, signs, disease, or laboratory abnormalities, but does not necessarily have a causal relationship with the investigational product.

Adverse Events of Special Interest (AESI) include:

- Ocular AESI:
  - Infectious endophthalmitis
  - Non-infectious endophthalmitis (eg, iritis, vitreous, iridocyclitis)
  - Elevated intraocular pressure (new AE with IOP >24 mmHg and no response to treatment, except transient IOP increase within 1 hour of study drug injection; AE with IOP ≥35 mmHg at any time requiring treatment)
  - Retinal detachment/tear
  - Retinal artery occlusion
  - Iatrogenic traumatic cataract
  - Retinal pigment epithelium detachment
- Systemic AESI:
  - Thromboembolic events (eg, venous thromboembolism, arterial thromboembolism).

Method for calculating percentage of subjects with AEs = number of subjects with adverse events/number of subjects in the safety set ×100%.

Based on the safety set, the analysis and summary are conducted by treatment group and the total number. The adverse event overview table will summarize the number (n), percentage (%) and adverse event cases of the following categories of adverse events. When calculating the number of subjects and percentage experiencing AEs, multiple occurrences of the same AE category in the same subject are counted only once. When calculating the frequency of AEs, if the same subject experiences multiple AEs within the same category, each occurrence is counted separately.

- Treatment-emergent adverse events (TEAEs)
  - Non-ocular TEAEs
  - Ocular TEAEs
    - ✧ TEAE in study eyes
    - ✧ TEAEs in non-study eyes
  - TEAEs of varying severity

- TEAEs related to study drug
- TEAEs related to ocular injections
- TEAEs related to protocol-required ophthalmic examinations
- TEAEs leading to dose reduction
  - ✧ TEAEs related to study drug and leading to dose reduction
  - ✧ TEAEs related to ocular injection and leading to dose reduction
- TEAEs leading to medication interruption
  - ✧ TEAEs related to study drug and leading to medication interruption
  - ✧ TEAEs related to ocular injection and leading to medication interruption
- TEAEs leading to medication discontinuation
  - ✧ TEAEs related to study drug and leading to medication discontinuation
  - ✧ TEAEs related to ocular injection and leading to medication discontinuation
- TEAEs leading to medication suspension
  - ✧ TEAEs related to study drug and leading to medication suspension
  - ✧ TEAEs related to ocular injections and leading to medication suspension

➢ Treatment-emergent serious adverse events (TESAEs)

- TESAEs related to study drug
- TESAEs related to ocular injections

➢ Treatment-emergent adverse events of special interest (TEAESIs)

The number (n), percentage (%), and number of adverse events in the following categories are then summarized by system organ class (SOC) and preferred term (PT) based on the safety set, by treatment group and the total number:

➢ Treatment-emergent adverse events (TEAEs)

- Non-ocular TEAEs
- Ocular TEAEs
  - ✧ TEAE in study eyes
  - ✧ TEAEs in non-study eyes
- TEAEs of varying severity

- TEAEs related to study drug
- TEAEs related to ocular injections
- TEAEs related to protocol-required ophthalmic examinations
- TEAEs leading to dose reduction
  - ✧ TEAEs related to study drug and leading to dose reduction
  - ✧ TEAEs related to ocular injection and leading to dose reduction
- TEAEs leading to medication interruption
  - ✧ TEAEs related to study drug and leading to medication interruption
  - ✧ TEAEs related to ocular injection and leading to medication interruption
- TEAEs leading to medication discontinuation
  - ✧ TEAEs related to study drug and leading to medication discontinuation
  - ✧ TEAEs related to ocular injection and leading to medication discontinuation
- TEAEs leading to medication suspension
  - ✧ TEAEs related to study drug and leading to medication suspension
  - ✧ TEAEs related to ocular injections and leading to medication suspension

➢ Treatment-emergent serious adverse events (TESAEs)

- TESAEs related to study drug
- TESAEs related to ocular injections

➢ Treatment-emergent Adverse Events of Special Interest (TEAESIs)

When calculating the number and percentage of subjects experiencing AEs, only one occurrence is counted for multiple AEs within the same SOC or PT for the same subject. When calculating the number of AE occurrences, multiple instances are counted for the same subject experiencing multiple AEs within the same SOC or PT. SOCs and PTs are listed in descending order based on the number of subjects experiencing AEs. If the counts are identical, they are sorted alphabetically.

List detailed information on subject adverse events (AEs), including the screening number/random number/group, the name of the adverse event, the location, the start date, the severity, the date of occurrence of the most serious degree, whether it is a serious adverse event (SAE)? is it an adverse event of special interest (AESI)?, AESI name, relationship with the study drug, relationship with eye injection, relationship with the ophthalmic examination required by the protocol, if it is determined to be related or likely to be related or likely to be related, please specify the name of

the ophthalmic examination, measures taken on the study drug, drug treatment, non-drug treatment, no measures taken, other cases, whether the adverse event caused the subject to withdraw from the study? , outcome, whether to continue, and end date.

List detailed information on the subject's SAE, including the screening number/random number/group, the name of the adverse event, the date of start of the SAE, death, life-threatening, resulting in significant or permanent disability or dysfunction, hospitalization or prolonged hospitalization, congenital abnormality or birth defect, important medical event/other.

5.7.3 Ophthalmic examination

The results of ophthalmic examination are analyzed separately according to the study eye and non-study eye, and only the study eye is analyzed if the data of the independent film reading center are analyzed.

Ophthalmic examinations include fundus examination, best corrected visual acuity-ETDRS chart, intraocular pressure (IOP), slit lamp biomicroscopy, optical coherence tomography (OCT), color fundus photography (CF), indocyanine green angiography (ICGA), and fluorescein fundus angiography (FFA).

Examination	Quantitative Results	Qualitative Results	Result Determination
Fundus examination	NA	NA	Normal, abnormal without clinical significance, abnormal with clinical significance, not examined
Best corrected visual acuity-ETDRS visual acuity chart	Best corrected visual acuity, spherical diopter, cylindrical diopter, ametropia spherical equivalent diopter	NA	NA
Intraocular pressure (IOP) test	Intraocular Pressure	NA	NA
Slit-lamp biomicroscopy	NA	Lens status, anterior chamber flare, anterior chamber cells, vitreous hemorrhage	NA
Optical Coherence Tomography (OCT)	Central Subfield Thickness (CST) *(analyzed based on data from the independent film reading center)*	NA	Normal, abnormal without clinical significance, abnormal with clinical significance, not examined
Color fundus photography (CF)	NA	Pupil patterns *(analyzed based on data from the*	Normal, abnormal without clinical significance,

		independent film reading center)	abnormal with clinical significance, not examined
Indocyanine green angiography (ICGA)	NA	NA	Normal, abnormal without clinical significance, abnormal with clinical significance, not examined
Fluorescein fundus angiography (FFA)	Total lesion area, total CNV area, total CNV leakage area *(analyzed based on data from the independent film reading center)*	Whether there is choroidal neovascularization (CNV), CNV classification, CNV distance from the fovea, and whether there is CNV leakage *(analyzed based on data from the independent film reading center)*	Normal, abnormal without clinical significance, abnormal with clinical significance, not examined

Based on the safety set, quantitatively describe the results of each ophthalmic examination item as continuous variables by treatment group for changes in outcomes at each visit and changes from baseline at each scheduled visit post-baseline; for qualitative results of each item, describe outcomes at each visit by treatment group as categorical variables.

Based on the safety set, cross-tabulate the changes in clinical significance determinations (normal, abnormal without clinical significance, abnormal with clinical significance, not examined) for each planned visit examination result by treatment group.

List ophthalmic examination results, including screening number/random number/group, examination items, visit/visit date, whether the examination was conducted, reason for non-examination, examination date/time, and examination details.

5.7.4 Laboratory tests

Laboratory tests include complete blood count, blood biochemistry, urinalysis, and glycated hemoglobin.

Complete Blood Count (Quantitative Results)	Blood Biochemistry (Quantitative Results)	Urinalysis (Quantitative/Qualitative Results)	Glycosylated Hemoglobin (Quantitative Results)
White blood cell count (WBC), red blood cell count (RBC), hemoglobin content (HGB), platelet count (PLAT), neutrophil count (NEUT), lymphocyte count	Total protein (PROT), albumin (ALB), total bilirubin (BILI), direct bilirubin (BILDIR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), urea nitrogen (UREAN), urea (UREA), uric acid (URAHCO3), creatinine (CREAT),	Quantitative results: pH (UPH) Qualitative results: urinary glucose (UGLUC), urinary protein (UPROT)	Glycosylated hemoglobin

(LYM), basophil count (BASO), eosinophil count (EOS)	blood glucose (bicarbonate) sodium (SODIUM), Chlorine (CL), Potassium (K), Calcium (CA), Magnesium (MG), Phosphorus (PHOS)		

For the convenience of statistical analysis, if there is a "<" or ">" symbol in the test result (for example, greater than or less than a certain quantitative limit value), the result of multiplying the limit value by 1 is used as the summary analysis.

Based on the safety set, statistically describe the quantitative results of each item in tests such as blood routine, blood biochemistry, and urine routine as continuous variables based on the changes in the results of each visit and the planned visits after baseline from baseline results by the treatment group; for the qualitative results of each item in tests such as urinalysis, statistically describe the results of each visit by the treatment group as categorical variables.

Based on the safety set, cross-tabulate the changes in clinical significance determinations (normal, abnormal without clinical significance, abnormal with clinical significance, not examined) for each planned visit examination result by treatment group.

List all test results, including screening number/random number/group, visit/visit date, whether to perform test, reason not to perform test, sampling date, test items, test results, clinical significance, and describe any abnormalities.

5.7.5 Vital signs

Vital signs include body temperature, systolic blood pressure, diastolic blood pressure, pulse, and respiratory rate.

Based on the safety set, statistically describe the results of each item in the vital signs examination as continuous variables according to the changes in the results of each visit and the planned visits after baseline from the baseline results by the treatment group.

Based on the safety set, cross-tabulate the changes in clinical significance determinations (normal, abnormal without clinical significance, abnormal with clinical significance, not examined) for each planned visit examination result by treatment group.

List all test results, including screening number/random number/group, visit/visit date, whether to perform test, reason not to perform test, test date, test items, and test results.

5.7.6 Physical examination

Physical examination includes general condition, skin and mucous membranes, lymph nodes, head and its organs, neck, chest, abdomen, spine and extremities, neurological evaluation, and others.

Based on the safety set, cross-tabulate the changes in clinical significance determinations (normal, abnormal without clinical significance, abnormal with clinical significance, not examined) for each planned visit examination result by treatment group.

List all test results, including screening number/random number/group, visit/visit date, whether to perform test, reason not to perform test, test date, test items, test results, and describe any abnormalities.

5.7.7 12-lead ECG

Based on the safety set, cross-tabulate the changes in clinical significance determinations (normal, abnormal without clinical significance, abnormal with clinical significance, not examined) for each planned visit examination result by treatment group.

List all test results, including screening number/random number/group, visit/visit date, whether to perform test, reason not to perform test, test date, test items, test results, clinical significance, and describe any abnormalities.

5.7.8 Blood pregnancy test

Based on the safety set, cross-tabulate the changes in clinical significance determinations (abnormal without clinical significance, abnormal with clinical significance, not examined) for each planned visit examination result by treatment group.

List all test results, including screening number/random number/group, visit/visit date, whether to perform test, and report content details.

5.7.9 Chest X-ray

Based on the safety set, cross-tabulate the changes in clinical significance determinations (abnormal without clinical significance, abnormal with clinical significance, not examined) for each planned visit examination result by treatment group.

List all test results, including screening number/random number/group, visit/visit date, whether to perform test, reason not to perform test, test method, test date, clinical significance, and describe any abnormalities.

5.8 Immunogenicity analysis

Positive immunogenicity is defined as negative ADA at baseline and positive ADA results after treatment, or positive ADA at baseline and at least a 4-fold increase in sample titration of positive ADA after treatment from baseline.

Based on the immunogenicity analysis set, summarize the number and percentage of immunogenicity-positive subjects at different visits (week 0, week 12, pre-dose at week 24, and final visit).

List all test results, including screening number/random number/group, visit/visit date, whether ADA/Nab blood collection is performed, planned blood collection time point, ADA test result, ADA titer, Nab test result, NAb titer, positive immunogenicity, and remarks.

6. Interim Analysis

No interim analysis is planned for this study.

7. Modifications to the Original Analysis Plan

There are no modifications to the original analysis plan in this study.

8. Statistical Analysis Table, Form and List Templates

Table, form and list templates used in the statistical analysis of this study are provided in separate documents.

9. References

1. National Medical Products Administration. *Data Management and Statistical Analysis Plan for Drug Clinical Trials*. December 2021
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. E9 Statistical Principles for Clinical Trials.
3. Addendum On Estimands And Sensitivity Analysis In Clinical Trials To The Guideline On Statistical Principles For Clinical Trials E9 (R1).
4. National Medical Products Administration. *Guidelines for Biostatistics of Drug Clinical Trials*. June 2016

Subject Screening Number: □□□□□

A Multicenter, Randomized, Double-blind Phase III Clinical Study Evaluating the Efficacy and Safety of TAB014 Versus Ranibizumab (Lucentis®) in Patients with Neovascular Age-Related Macular Degeneration

Informed Consent Form

Dear Sir/Madam:

Hello! We are conducting a multicenter, randomized, double-blind Phase III clinical study evaluating the efficacy and safety of TAB014 versus Ranibizumab (Lucentis®) in patients with neovascular age-related macular degeneration. Your condition may meet the inclusion criteria for this study, and therefore, we would like to invite you to participate in this study. This informed consent form will inform you about the study's purpose, procedures, benefits, risks, inconveniences, or discomforts. Please read it carefully and make a prudent decision regarding participation. During the investigator's explanation and discussion of this informed consent form, you may ask questions at any time and have him/her clarify any points you do not understand. You may discuss with your family, friends and your study physician before making your decision.

If you are currently participating in other clinical research, please inform your study physician or investigators.

This study is sponsored by ZhaoKe (Guangzhou) Ophthalmology Pharmaceutical Co., Ltd. and will be conducted concurrently at approximately 50–70 hospitals. A total of approximately 488 subjects will be included. Eligible subjects will be randomized in a 1:1 ratio to receive either TAB014 Ranibizumab (244 subjects receiving TAB014 and 244 Ranibizumab).

Should you decide to participate in this study, you must sign this informed consent form before any study-related procedures commence. The informed consent form is prepared in duplicate. Upon signing, one copy will be retained at the study site, and the other will be given to you for your records.

I. Study Background and Objectives

Age-related macular degeneration (AMD) is a common blinding eye disease currently affecting the quality of life of approximately 20 million individuals aged 65 and above worldwide. The incidence of AMD in China shows a marked upward trend, and its pathogenesis remains not very clear. Recent research has identified correlations between AMD and factors including age, gender, hypertension, chronic light damage, insufficient vitamin intake, high-density

lipoprotein levels, alcohol consumption, and smoking. Substantial evidence also indicates a genetic association. AMD can be classified into dry and wet types based on different fundus manifestations in patients. Wet AMD (wAMD), also termed neovascular AMD (nAMD), is characterized by choroidal neovascularization (CNV). Although less prevalent than dry AMD, it is the primary cause of vision loss in over 90% of AMD patients, posing a severe threat to visual function. This type of AMD progresses rapidly. Without treatment, more than 40% of patients will develop neovascularization in the other eye within five years after it occurs in one eye. In recent years, scholars at home and abroad have conducted extensive research on the treatment methods of wet AMD, aiming to treat nAMD by inhibiting the formation of new blood vessels and destroying the already formed new blood vessels.

Ranibizumab (Lucentis®), the first anti-vascular endothelial growth factor (VEGF) agent approved globally and in China for treating wet (neovascularization) age-related macular degeneration. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF), approved in many countries and regions for treating malignancies including colorectal cancer, non-small cell lung cancer, malignant glioma, renal cell carcinoma, ovarian cancer, and breast cancer. Currently, bevacizumab is widely used off-label in clinical practice for intravitreal injections to treat nAMD, diabetic macular edema, and other conditions. International clinical studies demonstrate favorable efficacy and safety profiles for bevacizumab in neovascular (wet) AMD, typically administered by a regular injection of 1.25 mg per month. Bevacizumab is comparatively inexpensive and demonstrates good clinical efficacy, but its indications do not include nAMD, thus presenting certain limitations in clinical application.

TAB014 is a VEGF antibody therapeutic developed by BioDlink International Company Limited for nAMD treatment. Pharmaceutical, nonclinical, and clinical study results indicate that intravenous administration of TAB014 injection exhibits pharmacokinetic, pharmacodynamic, and safety profiles consistent with marketed bevacizumab (Avastin®). TAB014 is currently classified as a Category 1 new biological drug and it has not been marketed either at home or abroad.

This randomized, double-blind, Ranibizumab-controlled study aims to evaluate the efficacy and safety of intravitreal TAB014 versus Ranibizumab (Lucentis®) in nAMD treatment and assess TAB014 immunogenicity.

This study is based on a double-blind design, meaning that throughout the study, neither you nor the study team knows which treatment group you are assigned to. This safeguards against potential bias influencing study outcomes. For urgent medical needs, the study team may rapidly unblind to identify whether TAB014 or Lucentis® is administered. Following emergency unblinding, the study physician may take appropriate therapeutic measures or provide proper care based on conventional experience. Your treatment assignment will only be disclosed when all participants complete the study and the data are obtained.

II. Who Is Eligible to Participate in This Study?

Main inclusion and exclusion criteria for this study are as follows:

1) Age ≥50 years;
2) Those with active subfoveal or paravascular choroidal neovascular lesions secondary to neovascular age-related macular degeneration;
3) Voluntary participation with demonstrated comprehension of this informed consent form and provision of written consent.

You will be excluded if the investigator deems you ineligible, including inability or unwillingness to comply with protocol requirements.

III. Study Plan and Implementation

This study includes the screening period, the randomization/baseline/first-dose period, the treatment period, and the final visit. The 28-day screening period involves assessments and examinations during the screening period if you agree to participate in this study and sign this informed consent form, including medical history collection, demographic data collection, measurement of height and weight, vital signs, complete blood count, blood biochemistry, glycated hemoglobin, blood pregnancy test (for women of childbearing age only), coagulation function, immunogenicity testing, and ophthalmic examinations. Study physicians will determine your eligibility based on the examination results. Eligible subjects who have passed screening will be randomized in a 1:1 ratio into two groups (randomization will be performed by computer using a randomization code program set by the statistician in accordance with a principle similar to drawing lots): the study group and the control group. The study group will receive TAB014, while the control group will receive Ranibizumab. If you are in the study group, the study eye (affected eye) will receive an intravitreal injection of 1.25 mg (0.05 mL) of TAB014. If you are in the control group, the study eye (affected eye) will receive an intravitreal injection of Ranibizumab (0.5 mg/0.05 mL). This study is expected to last 12 months, with both the study and control groups undergoing a 4-week treatment cycle. The final visit will be conducted 4 weeks after the last dose.

In addition, this study plans to conduct immunogenicity analysis in approximately 80 patients with nAMD in one eye who have not received anti-VEGF treatment in both eyes or the contralateral eye throughout the study, aiming to determine whether antibodies against TAB014 have been produced in the body. Based on the study progress and the study conditions at the site, patients with nAMD in one eye who have not received anti-VEGF treatment in both eyes or the contralateral eye throughout the study are required to participate in the immunogenicity study until the sponsor notifies the cessation of immunogenicity blood sampling.

The following outlines the study workflow (consult your study physician or staff if you have any questions):

Screening period (conducted within 28 days prior to randomization, Visit 1)

The purpose of the screening visit is to determine eligibility for study participation. The study physician will explain reasons for non-eligibility if applicable. The procedures and assessments below will be performed during screening period:

- Sign the informed consent form and verify eligibility;
- Inquire about medical history, allergy history, smoking or drinking habits, and essential personal information;
- Measure height and weight (acceptable within 28 days prior to randomization);
- Physical examination (acceptable within 28 days prior to randomization);
- Record vital signs (temperature, blood pressure, pulse, respiratory rate; acceptable within 28 days prior to randomization);
- Conduct laboratory tests: blood (CBC, biochemistry, coagulation), urine (urinalysis; acceptable within 14 days prior to randomization);
- Perform HbA1c test (acceptable within 28 days prior to randomization);
- Pregnancy test (blood collection required; applicable only to women of childbearing potential [as determined by the study physician]; to be performed within 28 days prior to randomization);
- 12-lead ECG (acceptable within 14 days prior to randomization);
- Chest X-ray (AP/lateral views; acceptable within 28 days prior to randomization. If the subject has a CT scan result within 28 days prior to randomization, the CT result may be accepted as a substitute for the chest X-ray result.
- Infectious disease screening (blood collection required, including tests for AIDS, hepatitis B, hepatitis C and syphilis, acceptable within 3 months prior to randomization);

Ophthalmic examinations include:

- Best corrected visual acuity test (for both eyes, using the ETDRS [Early Treatment Diabetic Retinopathy Study] chart, acceptable within 14 days prior to randomization);
- Intraocular pressure measurement, slit-lamp examination, fundus examination (for both eyes; acceptable within 14 days prior to randomization)
- Optical coherence tomography (OCT), indocyanine green angiography (ICGA), fluorescein fundus angiography (FFA), color fundus photography (for both eyes; acceptable within 14 days prior to randomization)
- Monitor concomitant medications/therapies.

Randomization/baseline/first-dose administration (Visit 2)

You will be randomized after obtaining your signed informed consent form, completing all necessary screening procedures, and being deemed eligible for study participation by the study physician or authorized staff. All eligible subjects must be randomized in a 1:1 ratio through the randomization system. You have a 50% probability of assignment to TAB014 or Ranibizumab treatment. The first dose must be administered on the day of randomization. The following outlines the procedures and assessments you need to complete during randomization/baseline/first dose period.

For study procedures that require screening period and randomization/baseline/first dose period to be repeated while maintaining identical pre-randomization period requirements, such procedures may be performed only once during the screening and baseline phases (e.g., if laboratory tests are required during both screening and baseline period, and results from within 14 days prior to randomization are acceptable for both phases, laboratory testing may be performed only once during the combined screening period and baseline period).

- Physical examination (acceptable within 7 days prior to randomization);
- Measure vital signs (including body temperature, blood pressure, pulse, and respiratory rate; vital signs should be checked within 24 h prior to injection and 60 (±30) min after injection);
- Conduct laboratory tests: blood (CBC, biochemistry, coagulation), urine (urinalysis; acceptable within 14 days prior to randomization);
- 12-lead ECG (acceptable within 14 days prior to randomization);
- Immunogenicity test: Blood samples of 5 mL should be collected from the subjects undergoing immunogenicity test within 2 h prior to dosing.

Ophthalmic examinations include:

- Best corrected visual acuity test (for both eyes, using the ETDRS [Early Treatment Diabetic Retinopathy Study] chart, acceptable within 3 days prior to randomization);
- Intraocular pressure measurement, slit-lamp examination, fundus examination (for both eyes; acceptable within 14 days prior to randomization)
- Optical coherence tomography (OCT), indocyanine green angiography (ICGA), fluorescein fundus angiography (FFA), color fundus photography (for both eyes; acceptable within 14 days prior to randomization);
- Post-injection assessment: Intraocular pressure in both eyes should be measured after each administration of TAB014/Ranibizumab (Lucentis®) (within 60 (±10) min post-injection). Assess whether the study eye can count fingers or perceive hand motions post-injection;

- Monitor concomitant medications/therapies;
- Record adverse events (AEs).

Treatment period (Visit 3 to Visit 14)

This phase spans approximately 52 weeks, with dosing every 4 weeks. One treatment cycle lasts for 28 days; visits occur on the day of investigational product administration. A total of 13 doses will be administered: first dose on randomization day and 12 additional doses during the treatment period.

(1) Irrespective of treatment arm assignment, the study physician will designate one eye suitable for study observation as the **"study eye"** to receive intravitreal injections every 4 weeks. The standard dose is 1.25 mg/0.05 mL of TAB014 monoclonal antibody injection and 0.5 mg/0.05 mL of Ranibizumab injection.

(2) For the contralateral eye not receiving study treatment (**non-study eye**), if an ocular disease develops in this eye and the study physician deems treatment necessary, the treatment permitted by the study can also be carried out after 30 days of randomization based on the judgment of the study physician. If wet age-related macular degeneration (wAMD) is diagnosed in the **non-study eye**, symptomatic treatment may be administered at the study physician's discretion, but no earlier than 30 days post-randomization.

(3) **The 12 treatment-period visits occur on Day 1 of each treatment cycle (i.e., day of investigational product administration)** with a ±7-day visit window allowed. The investigational product will be administered at each visit after the study physician determines that the patient meets the dosing criteria.

Visit X	3	4	5	6	7	8	9	10	11	12	13	14
Day 1 of Week X	4	8	12	16	20	24	28	32	36	40	44	48
Dosing No.	2	3	4	5	6	7	8	9	10	11	12	13

(4) Investigator may temporarily interrupt treatment if adverse events occur during therapy; resumption of treatment is at the discretion of the study physician. If treatment interruption occurs, the subject will be arranged for the next visit.

Visit 3 to **Visit 14**: Starting from **Visit 3**, you need to visit the site every 4 weeks to receive the study drug and undergo the visit procedures on the same day, until Visit 14. Required examinations and procedures during these visits include:

- Administration of study treatment (TAB014/Ranibizumab);
- Physical examination (only during **Visit 5**, **Visit 8**, and **Visit 11**; acceptable within 7 days prior to randomization);
- Vital sign measurements (within 24 hours pre-dose and 60 (±30) min post-dose);

- Laboratory tests (only during **Visit 5**, **Visit 8**, and **Visit 11** including CBC, blood biochemistry, coagulation function, and urinalysis, to be performed within 7 days before administration);
- 12-lead ECG (only during **Visit 5**, **Visit 8**, and **Visit 11** ; acceptable within 7 days prior to randomization);
- Monitoring of adverse events and concomitant medications/therapies;
- **Immunogenicity test** (blood collection during **Visit 5** and **Visit 8** pre-dose; planned to be conducted in approximately 80 subjects with nAMD in one eye who had not received anti-VEGF treatment in both eyes or the contralateral eye throughout the study period).

Ophthalmic examinations include:

- Best corrected visual acuity test (for both eyes, using the ETDRS [Early Treatment Diabetic Retinopathy Study] chart, acceptable within 3 days prior to each dosing);
- Intraocular pressure measurement (for both eyes, acceptable within 3 days prior to each dosing; 1 additional measurement within [approximately 60 min post-administration] of TAB014/Lucentis®);
- Slit-lamp examination (for both eyes; acceptable within 3 days prior to each dosing);
- Fundus examination (for both eyes; acceptable within 3 days prior to each dosing);
- Optical coherence tomography (OCT) (for both eyes; acceptable within 3 days prior to each dosing);
- Indocyanine green angiography (ICGA), fluorescein fundus angiography (FFA), color fundus photography (for both eyes; performed only during **Visit 5** and **Visit 8** ; acceptable within 14 days prior to dosing).
- Post-injection assessment: Intraocular pressure in both eyes should be measured after each administration of TAB014/Ranibizumab (Lucentis®) (within 60 (±10) min post-injection). Assess whether the study eye can count fingers or perceive hand motions post-injection.

Final Visit (conducted 4 weeks after the last dose [i.e., Day 1 of Week 52]):

- Physical examination;
- Vital sign measurements;
- Laboratory tests (CBC, blood biochemistry, coagulation function, urinalysis);
- Pregnancy examination (blood collection required, only applicable to women of childbearing age [as determined by the study physician]);
- 12-lead ECG;

- Chest X-ray (including anterior-posterior and lateral views);
- Monitoring of adverse events and concomitant medications/therapies;
- **Immunogenicity test** (planned to be conducted in approximately 80 subjects with nAMD in one eye who had not received anti-VEGF treatment in both eyes or the contralateral eye throughout the study period).

Ophthalmic examinations include:

- Best corrected visual acuity test (for both eyes, using the ETDRS [Early Treatment Diabetic Retinopathy Study] chart);
- Intraocular pressure measurement and optical coherence tomography (OCT) (for both eyes);
- Slit-lamp and fundus examinations (for both eyes);
- indocyanine green angiography (ICGA), fluorescein fundus angiography (FFA), color fundus photography (for both eyes).

Biological sample collection (approximately 80 subjects participating in immunogenicity analysis only)

Blood samples for testing (CBC, blood biochemistry, coagulation function, pregnancy test, infectious disease screening, immunogenicity) will be collected per the schedule. The approximate blood volume collected for tests is as follows: 2 mL for CBC, 5 mL for blood biochemistry, 2 mL for HbA1c, 2 mL for coagulation, 4 mL for pregnancy test, 4 mL for infectious disease screening, and 5 mL for immunogenicity test.

Subjects in immunogenicity studies will have total blood draws of approximately 88 mL(including approximately 68 mL for study procedures and approximately 20 mL for anti-TAB014 antibody assessment). Subjects not in immunogenicity studies will have total blood draws of approximately 68 mL for study procedures.

Duration of study participation

Participation duration is approximately 12 months. A total of 15 site visits are required throughout the study. The screening period will last no more than 28 days; the treatment period will be approximately 52 weeks, with dosing administered every 4 weeks; the final visit will occur 4 weeks after the last dose. Hospitalization decisions and duration are determined by the study physician based on clinical need.

Post-study drug accessibility

As this is a clinical study, investigational products TAB014 and Ranibizumab (Lucentis®) will only be provided during study participation and discontinued thereafter.

IV. Impact on Subject's Daily Life

When deciding whether to participate in this study, please carefully consider its potential impact on your daily work and family life, as well as the time commitment and transportation arrangements required for each follow-up visit. If you have any questions regarding the examinations and procedures involved in the study, you may consult with us.

During the study period, the use of any medication for treating AMD other than the study drug TAB014 or Ranibizumab is not allowed (except if investigator deems treatment necessary for the non-study eye ≥30 days post-first dose in the study eye).Any use of other medications to treat AMD must be disclosed to the study physician.

To ensure safety and data validity, participation in any other clinical studies involving drugs or medical devices is not allowed during the study period.

Prohibited drugs and treatments

- The following treatments are not permitted in the study eye throughout the study:

  a) External beam radiation therapy targeting the eye or head for AMD, focal laser photocoagulation, and trans-pupillary thermotherapy intervention.

  b) Intraocular surgeries including anterior and posterior segment procedures such as cataract surgery, glaucoma filtration surgery, vitrectomy, and YAG laser posterior capsulotomy.

  c) Intraocular/periocular corticosteroids (excluding topical preparations) and intraocular steroid implants (e.g., dexamethasone, fluocinolone acetonide).

  d) Anti-angiogenic drugs not included in this study (including any anti-VEGF agents such as pegaptanib, bevacizumab, aflibercept, conbercept, and brolucizumab).

  e) Ophthalmic solutions indicated for fundus hemorrhage, macular degeneration, etc. (e.g., Esculin and Digitalisglycosides Eye Drops).

- The following medications are not permitted in the non-study eye within 30 days after randomization of the study eye throughout the study:

  Any anti-angiogenic agents (including Ranibizumab, pegaptanib, bevacizumab, aflibercept, conbercept, and brolucizumab, etc.).

- The following drugs (systemic administration) are not allowed throughout the study:

  a) Anti-VEGF agents (e.g., sorafenib, sunitinib, and bevacizumab, etc.).

  b) Traditional Chinese medicines indicated for fundus hemorrhage and macular degeneration (e.g., Hemostasis and Brightening Eyes Tablets).

c) Corticosteroids. Intranasal, inhaled, topical dermatological, intra-articular, perianal corticosteroids, and short-term (continuous use for <2 weeks) oral corticosteroids are permitted.

d) Drugs known to be toxic to the lens, retina, or optic nerve include deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines, and ethambutol.

e) Additionally, the use of any other investigational products or investigational interventions not part of this study (e.g., isovolumetric hemodilution, intravitreal tissue-type plasminogen activator) is prohibited throughout the study.

V. Potential Benefits

Participation in this study is entirely voluntary. Potential benefits you may gain from this study include:

You may receive therapeutic benefit for wet age-related macular degeneration by participating in this study, although we cannot guarantee improvement in your health condition. We hope the information gained from your participation in this study will benefit patients with the same condition in the future. Should you choose not to participate, your physician will recommend alternative treatment options.

VI. Possible Adverse Reactions, Risks and Discomforts

It is crucial to immediately notify your physician of any discomfort, new symptoms, or unexpected events occurring during observation, regardless of their relationship to the study drug. Your physician will assess and provide medical treatment, potentially prescribing additional medications to control side effects. The study drug may be discontinued and you may withdraw from the study if you or the study physician deem side effects intolerable.

Adverse reactions may occur with any medication. The control group receives the marketed product Ranibizumab. Refer to its prescribing information for potential adverse reactions. The following describes potential adverse reactions specific to the investigational product:

Ocular adverse reactions may include: endophthalmitis, elevated intraocular pressure, conjunctival hemorrhage, foreign body sensation, visual disturbance, corneal abrasion, lens injury, retinal detachment, retinal artery occlusion, submacular hemorrhage, and retinal pigment epithelial detachment; systemic adverse reactions may include non-ocular hemorrhage, hypertension, and thromboembolic events. Serious injection-related adverse reactions occur at <0.1% frequency and include endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

Risks of blood draw

Risks associated with blood draws from the arm include transient discomfort and/or bruising.

In extremely rare cases, individuals may experience blood clotting or fainting.

Reproductive risks

No studies on reproductive toxicity have been conducted for this product.

If you become pregnant or suspect you might be pregnant during the study, you should immediately inform the investigator, who will discuss with you what steps to take.

Other risks

Currently unforeseeable risks, discomforts, drug interactions, or adverse reactions may also occur.

VII. Other Treatment Options

You may consider the following alternative treatment options:

- Other approved therapies for neovascular age-related macular degeneration as recommended by your physician, such as Ranibizumab, aflibercept, or conbercept.
- You may participate in other studies investigating treatments for neovascular age-related macular degeneration.

You may discuss these alternative treatments with your doctor to determine whether you wish to participate in this study.

Should you decline participation, your physician will still recommend other treatments and medications that are appropriate for you.

VIII. Voluntary Participation and Withdrawal Rights

Participation in this study is entirely voluntary. You may refuse participation without prejudice to current or future medical care if you do not want to participate in the study. You may change your mind at any time and inform the investigator that you wish to withdraw from the study after providing consent. Withdrawal will not result in discrimination, retaliation, or affect access to standard medical care. Upon deciding to withdraw, it is advisable to promptly notify your study physician, who can then provide recommendations and guidance regarding your health condition.

You will be withdrawn if any of the following occur: 1) Continued participation poses health risks according to the judgment of the study physician; 2) Concurrent illnesses severely interfere with clinical assessments or necessitate treatment discontinuation according to the judgment of the study physician; 3) The sponsor explicitly requests treatment discontinuation; 4) You fail to comply with the study protocol; 5) Pregnancy occurs; 6) You withdraw your informed consent; 7) You cannot be reached and the study physician fails to contact you or your family; 8) Regulatory authorities require termination.

If you withdraw from the study for any reason, you may be asked about the use of the investigational product. Laboratory tests may be requested if the physician deems it necessary.

If you choose to participate in this observation, we encourage completion of the entire study period.

The Sponsor or regulatory authorities may terminate the study prematurely. Should this study be terminated early, we will notify you promptly. Your study physician will provide recommendations for your next treatment plan based on your health status.

Should you withdraw from the study, we have a final follow-up plan in place for safety reasons. You have the right to decline. We may re-contact you if new information related to your health and rights is discovered after your withdrawal.

In principle, the investigator will securely retain your information until its final destruction after your withdrawal, during which time it will not be further used or disclosed. However, in the following extremely rare circumstances, investigators may continue to use or disclose your information even if you have withdrawn from the study or the study has been concluded: removing your information would compromise the scientific integrity of the research findings or the evaluation of data security; providing limited information for research, teaching, or other activities (such information will not include your name, ID number, or any other personally identifiable details); when government regulatory authorities require oversight of the study, they may request access to all research data, which would include the information related to your participation at the time.

IX. Study Participation Costs

The investigational products will be provided at no cost by the Sponsor in this study.

The Sponsor, ZhaoKe (Guangzhou) Ophthalmology Pharmaceutical Co., Ltd., will cover the costs of all study-related examinations you undergo during your participation and will provide the study drug free of charge. The free examination items in this study include the required refraction and visual acuity tests (BCVA), slit-lamp examination, fundus photography, OCT, fundus angiography, complete blood count, urinalysis, blood biochemistry, coagulation function, infection screening, electrocardiogram, chest X-ray, and pregnancy tests for women of childbearing age. The relevant tests conducted in this study are intended to evaluate the efficacy and safety of the drug. No additional tests unrelated to the disease condition or safety will be performed during the study.

Participants will receive free study drugs, protocol-specified laboratory tests, and transportation subsidies of RMB300 per visit (15 visits total). Those undergoing immunogenicity blood sampling will receive RMB400 per nutritional allowance per sampling (4 samplings total). Payments will be made according to actual visit frequency and institutional procedures.

The study physician will determine causality between adverse events occurring from study

entry to completion and either study drugs or protocol-mandated procedures. In the event that adverse events caused by the investigational product or diagnostic procedures required by the study protocol result in harm to you, you will receive active treatment at your study hospital. The Sponsor has purchased insurance for this study and will cover the medical expenses incurred as well as any financial compensation mandated by relevant laws. Non-study-related costs will not be covered by the Sponsor.

X. Specimen Handling

Blood biochemistry, hematology, coagulation, pregnancy, and urinalysis testing will be performed at the clinical research site using provided specimens. Any blood and urine remaining after the study will be destroyed.

The immunogenic blood samples collected during the study will be transferred to the analysis and testing organization Pharmaron (Shanghai) Co., Ltd. (3/F, Block C, Jinke Center, No. 2727 Jinke Road, Pudong New Area, Shanghai) for analysis. After analysis, the remaining specimens will be destroyed following market release. If additional analyses beyond the protocol are required for these specimens, and such analyses were unforeseeable at the time you signed the informed consent form, every effort will be made to notify you in advance. You may permit or decline such additional testing. Biological specimens will not contain personally identifiable information.

XI. Management of Study-related Injuries

During your participation in this study, please promptly inform the investigator if your health condition is affected. We will take necessary medical measures. In accordance with laws and regulations in China, the Sponsor of this study will bear the corresponding medical expenses and provide appropriate economic compensation for any research-related injuries. However, treatments and examinations required for other concurrent diseases will not be covered under this provision.

XII. Study Participation Requirements

1. Provide accurate medical history and current medical condition.
2. Inform the study physician of any health issues that arise during the study period.
3. Disclose to the study physician any medications, vitamins, or herbal supplements you are taking during the study period.
4. Do not take any medications or therapies (including prescription, over-the-counter, vitamin, or herbal products), unless authorized by your study physician.
5. Attend all scheduled visits.
6. Do not participate in other clinical trials.

7. Employ appropriate contraception measures.
8. Follow all instructions from the investigator and the study physician.
9. Feel free to ask if anything is unclear.

XIII. Confidentiality of Participant Information

If you decide to participate in this study, your participation and personal information within the study will be kept confidential. Blood/urine specimens will be labeled with study codes rather than names. Personally identifiable information will not be disclosed to non-study personnel without your permission. All study personnel and the Sponsor are required to keep your identity confidential. Your records will be stored in locked cabinets and are accessible only to the investigators. To ensure compliance with regulations, government authorities, ethics committee members, sponsor-appointed monitors, and auditors may access your personal data at the study site as necessary and in accordance with applicable requirements. Upon publication of the study results, no personally identifiable information will be disclosed.

XIV. New Study-related Information

We may obtain new information about the treatment and may need to obtain your informed consent again during the study. You will be promptly notified to decide whether to continue participation or withdraw from the study.

XV. Who to Contact with Questions or Concerns

If you have any study-related questions, please contact your assigned physician _____ at the following number:_____.

For questions pertaining to your rights as a participant, please contact the Hospital Ethics Committee for Drug Clinical Trials at the following number:_____.

Informed Consent Form • Signature Page for Consent

Subject Consent Statement:

I have been fully informed of the background, objectives, procedures, risks, and benefits of **"A Multicenter, Randomized, Double-blind Phase III Clinical Study Evaluating the Efficacy and Safety of TAB014 Versus Ranibizumab (Lucentis®) in Patients with Neovascular Age-Related Macular Degeneration"**. I was afforded sufficient time and opportunity to ask questions, and all responses were satisfactory. I was informed that I would receive the original copy of this informed consent form bearing both my signature and that of the investigator. I was also informed who to contact when I have questions or wish to obtain further information. I have read this informed consent form and agree to participate in this study, understanding that:

I may consult the investigator for additional information at any time;

I may withdraw from this study at any time without prejudice, discrimination, or effect on my medical care and rights.

Should my medical condition change requiring concomitant medications, I will either consult with the investigator prior to initiation or truthfully report such usage afterwards.

If I meet the criteria for immunogenicity blood sampling:

□ **I consent to participate in immunogenicity blood sampling.**

□ **I do not consent to participate in immunogenicity blood sampling.**

□ **Not applicable.**

I hereby provide my informed consent to participate in this study and commit to following the investigator's instructions to the best of my ability.

Subject's name (in regular script):

Signature of subject: Date:

Subject's phone number:

Name of legal representative (in regular script):

Signature of legal representative: Date:

Relationship with the subject:

Legal representative's phone number:

I confirm that the information in this informed consent document has been accurately explained and that the subject and/or legal representative fully comprehends the content. The subject voluntarily consents to participate in this study.

Name of the impartial witness (in regular script):

Signature of the impartial witness: Date:

Phone number of the impartial witness:

Investigator's Statement of Explanation:

I have explained to the subject (and/or legal representative) the background, objectives, procedures, risks, and benefits of **"A Multicenter, Randomized, Double-blind Phase III Clinical Study Evaluating the Efficacy and Safety of TAB014 Versus Ranibizumab (Lucentis®) in Patients with Neovascular Age-Related Macular Degeneration"**, and provided him/her with sufficient time to read the informed consent form, discuss it with others, and address any questions regarding the study. I have informed the subject of the contact information to reach out to in case of concerns. I have informed the subject (or legal representative) that he/she may withdraw from the study at any time during its duration without needing to provide a reason.

Investigator's name (in regular script):

Signature of investigator: Date:

Phone number: