NCT05816070

Drug Name	IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution)
Protocol	IVIEW-1201-BAC-II
Version	2.0
Date	Oct 10th 2022

A Phase II, Multi-Center, Randomized, Parallel-Controlled Study to Evaluate the Clinical Efficacy and Safety of IVIEW-1201 (1.0%PVP-I) Gel Forming Ophthalmic Sterile Solution Compared to Ofloxacin Eye Drops in the Treatment of Acute Bacterial Conjunctivitis

Clinical Study Protocol：IVIEW-1201-BAC-II

Title	A Phase II, Multi-Center, Randomized, Parallel-Controlled Study to Evaluate the Clinical Efficacy and Safety of IVIEW-1201 (1.0%PVP-I) Gel Forming Ophthalmic Sterile Solution Compared to Ofloxacin Eye Drops in the Treatment of Acute Bacterial Conjunctivitis.
Investigational Product	IVIEW-1201(1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution)
Sponsor	IVIEW Therapeutics, Inc.
Address	5 Cedar Brook Drive, Cranbury, New Jersey 08512
Domestic Clinical Trial Execution Agency	IVIEW Pharmaceutical (Zhuhai) CO., LTD
Address	
Phase	II
Project Leader	
Contact	

SIGNATURE PAGE

Sponsor

We will be responsible for initiating, applying for, organizing, funding and auditing this clinical trial in accordance with the "Good Clinical Practice for Drugs" and other regulations. And conscientiously perform the responsibilities of the applicant unit in accordance with the "Drug Registration Management Measures" and other relevant regulations, and provide relevant information, research drugs, trial funds, etc. in accordance with the clinical trial agreement.

Sponsor IVIEW Therapeutics, Inc.； IVIEW Pharmaceutical (Zhuhai) CO., LTD

Project Leader (Signature)： Date： YYMMDD

SIGNATURE PAGE

Investigator

I have read this protocol and I agree to conduct this clinical trial in accordance with the design and provisions of this protocol. I will conscientiously perform my duties as a researcher in accordance with the "Good Clinical Practice for Drugs" and other regulations. I will ensure the accuracy, authenticity, completeness and reliability of the trial data, and accept the audit and inspection by monitors and auditors assigned by the contract research organization/sponsor and the drug supervision and administration department.

I agree to keep confidential all information related to this clinical study (including this clinical study plan) provided by the sponsor IVIEW Therapeutics, Inc. and IVIEW Pharmaceuticals (Zhuhai) Co., Ltd. I declare that there is no financial interest relationship between myself, my family, this research unit and the sponsor.

Site Eye Hospital Affiliated to Shandong First Medical University (Shandong Eye Hospital)

Principle Investigator (Signature)： Date： YYMMDD

SIGNATURE PAGE

Central Laboratory

I have read this study plan and agree to its contents. I will conduct the study in strict accordance with the study plan and the Good Clinical Practice for Drugs and other regulations, and conscientiously perform my biological sample testing duties.I agree to keep confidential all information received or obtained during the trial related to this project.

Central Laboratory Suzhou Xishan Biotechnology Co., Ltd.

Person in Charge(Signature)： Date： YYMMDD

SIGNATURE PAGE

Contract Research Organization (CRO)

I have read this protocol. I will appoint a qualified monitor in accordance with the Good Clinical Practice for Drugs and other regulations, and require the monitor to perform the corresponding duties, including ensuring that the rights and interests of the subjects in the clinical trial are protected, and that the data in the research records and reports are true, accurate, complete and correct. Ensure that the study complies with the approved protocol and relevant regulations. I agree to keep confidential all information related to this protocol received or obtained during the trial.

CRO Proswell Medical

Person in Charge(Signature)： Date： YYMMDD

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SYNOPSIS

Title	A Phase II, Multi-Center, Randomized, Parallel-Controlled Study to Evaluate the Clinical Efficacy and Safety of IVIEW-1201 (1.0%PVP-I) Gel Forming Ophthalmic Sterile Solution Compared to Ofloxacin Eye Drops in the Treatment of Acute Bacterial Conjunctivitis.
Sponsor	IVIEW Therapeutics, Inc.
Domestic Clinical Trial Execution Agency	IVIEW Pharmaceutical (Zhuhai) CO., LTD
Purpose	To explore the efficacy and safety of IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution) in the treatment of acute bacterial conjunctivitis to provide a basis for the Phase III clinical trial.
Study Design	Mult-center, randomized, parallel-group, positive-controlled.
Criteria	**Inclusion Criteria:** Potential study subjects must meet all of the following inclusion criteria to be enrolled in this study. 1.Volunteered to participate in the study and signed the Informed Consent Form after receiving a verbal and written explanation of this clinical trial. In cases where the subject is unable to sign the Informed Consent Form, his/her guardian may sign in accordance with relevant regulations. 2.Aged above 15 (inclusive), male or female. 3.A diagnosis of acute bacterial conjunctivitis based on clinical observations: a) a score of ≥1 for bulbar conjunctival congestion and ≥1 for conjunctival secretion/exudation in at least one eye (same eye); and b) increased purulent, mucopurulent or mucopurulent secretions are observed in the conjunctival sac of the affected eye in all patients. Willing to cooperate in the completion of all procedures and visits required for the trial. **Exclusion Criteria:** Subjects are excluded from the study if any of the following exclusion criteria are met. 1. Patients with systemic or ocular diseases, or functional disorders with comorbidities, or structural abnormalities that, in the judgment of the investigator, could adversely affect the course or results of the trial (e.g. hyperthyroidism, hepatitis, acute and chronic renal insufficiency). 2. Those who have a history of allergy or serious adverse reactions to any component of IVIEW-1201 (1.0% povidone-iodine ophthalmic gel sterile solution) and Ofloxacin Eye Drops; have a history of allergy or serious adverse reactions to quinolones; or have a cumulative total of three or more allergies to other drugs, food and environment; or who are prone to allergic symptoms such as rash and urticaria; 3. Symptoms or signs of bacterial conjunctivitis for more than 72 hours prior to screening;

	4. Suspected fungal, viral or acanthamoeba infections based on clinical observations; 5. Those with severe keratitis or corneal opacity affecting the study results; 6. Active inflammation of the cornea, iris, or anterior chamber; 7. Corrected visual acuity of less than 0.2 in either eye; 8. History of eye surgery within 3 months prior to screening; 9. Those who have a history of acute or chronic dacryocystitis; 10. Those who need to wear corneal contact lenses during the trial; 11. Those who have used antibiotic eye drops or glucocorticoid eye drops within 14 days, and oral or intravenous antibiotics within 72 hours prior to screening; 12. Systemic use of steroidal drugs within 14 days prior to screening. Local use of eye steroidal drugs or nonsteroidalanti-inflammatory drugs (NSAIDs) within 7 days before enrollment (nasally or bronchially inhaled steroidal drugs are not allowed during the study); 13. Those with co-infections requiring treatment with other anti-infective drugs in the study; 14. Those who are using other drugs that may interfere with the efficacy or safety evaluation of the drug; 15. Participation in other interventional clinical trials within 30 days prior to the study; 16. Pregnant or lactating women, women with positive pregnancy tests and those planning to become pregnant (including male subjects); subjects who do not take effective contraceptive measures within 1 month before enrollment, or subjects (including male subjects) who are unwilling to take effective contraceptive measures within the next 6 months. 17. Other conditions or illnesses judged by the clinical investigator to be unsuitable for enrollment.
Sample Size	120 cases, 60 cases in the treatment group and 60 cases in the control group.
Investigational Drug	IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution): usually a reddish brown thick liquid or gel, which becomes a brown uniform transparent solution after shaking. Specification: 5g: 5mg (based on I2), Bio-Concept Laboratorie (USA)
Comparator Drug	Ofloxacin Eye Drops (Tarivid®) Slightly yellowish green clear solution, specification: 5ml:15mg, Santen Pharmaceutical (China) Co., Ltd.
Administration Method	**IVIEW-1201** Shake well before use, 1 drop/eye/time in the affected eye. The drug shall be administered once at the study site on Day 1, and then at least once every 3 hours until bedtime, up to a maximum of 4 doses; The drug shall be administered 4 doses on Day 2, with an interval of at least 3 hours; The drug shall be administered 3 doses a day from Day 3 to Day 7, with an interval of at least 3 hours, with duration of administration of 7 days. **Ofloxacin Eye Drops (Tarivid®)** Shake well before use, 1 drop/eye/time in the affected eye. The drug shall be administered once at the study site on Day 1, and then at least once every 3 hours until bedtime, up to a maximum of 4 doses; The drug shall be administered 4 doses on Day 2, with an interval of at least 3

	hours; The drug shall be administered 3 doses a day from Day 3 to Day 7, with an interval of at least 3 hours, with duration of administration of 7 days. **Administration Route** Sit or lie on back, tilt head back slightly, look up, place the test drug bottle mouth close to the eyelid of the affected eye, drop 1 drop, then gently close eyes and press the inner canthus of the eye with fingers for 1 to 2 minutes, then rest for about 5 minutes. If the test drug is not completely dropped into the eye during administration, add one drop. Among them, the test group needs to gently shake the drug solution before instilling it before use.
Treatment of Newly Infected eyes	If a subject suffers from monocular disease at Visit 1 and the other healthy eye becomes infected and develops bacterial conjunctivitis after Visit 1 during the study, the newly infected eye shall be treated with the investigational drug of the subject's group, following the prescribed administration regimen for the group, i.e. "the drug shall be administered once in the study site on Day 1, and then at least once every 3 hours until bedtime, up to a maximum of 4 doses; the drug shall be administered 4 doses on Day 2, with an interval of at least 3 hours; the drug shall be administered 3 doses a day from Day 3 to Day 7, with an interval of at least 3 hours, with duration of administration of 7 days", until Visit 5. At Visit 5, if the investigator determines that the newly infected eye still requires continued treatment based on the subject's signs and symptoms, the investigator will determine the specific treatment regimen after the subject is removed from the study, but the use of IVIEW-1201 (1.0% povidone-iodine ophthalmic gel sterile solution) should be discontinued. Newly infected eyes are not included in the group test, but normal secretions are taken for bacterial culture.
Visits	This study will be divided into 5 visit phases, namely Visit 1 (screening/baseline period, Day 1), Visit 2 (Day 3), Visit 3 (Day 6), Visit 4/End of Treament(EOT) (Day 8 ±1 day) and Visit 5/End of Study(EOS) (Day 14±1 day).
Efficacy Evaluation	**Primary outcomes** Clinical cure rate: The proportion of subjects with a score of 0 (on a 3-point scale) for bulbar conjunctival congestion and 0 (on a 3-point scale) for conjunctival secretion/exudation at Visit 4 (Day 8±1 day) and Visit 5 (Day 14±1 day). **Secondary outcomes** Clearance rate: The clearance rate of each major pathogenic bacteria at Visit 2, 3, 4 and 5: Stratified analysis shall be conducted according to the type of pathogenic bacteria and the visit time point, and the clearance rate of each kind of bacteria by the investigational drug at different times shall be calculated. Bacterial clearance is defined as positive bacterial culture at baseline and negative bacterial culture at the last visit. Bacterial clearance rate = (number of subjects cleared + number of subjects assumed to be cleared) / total number of subjects enrolled × 100%. **Exploratory outcomes** Mean clinical improvement rate at Visit 2, 3, 4 and 5: Clinical improvement rate = (pre-treatment score - post-treatment score) / pre-treatment score x

	100%. The score of symptoms and signs is the sum of the scores for pain, foreign body sensation, photophobia, tearing, conjunctival congestion, conjunctival secretion/exudation and conjunctival edema. Total effective rate (%) at Visit 2, 3, 4 and 5: Total effective rate (%) = (number of subjects cured+ number of subjects markedly effective) / total number of subjects available for evaluation of efficacy × 100%. Comprehensive efficacy evaluation: defined as cured, markedly effective, effective and ineffective; Calculate the total effective rate; See Appendix 2 for judgment criteria.
Safety Evaluation	Including adverse events/serious adverse events, clinically significant changes in ocular and systemic symptoms and signs before and after treatment.
Statistical analysis method	**Selection of statistical analysis data set** Full Analysis Set (FAS): All subjects randomized and for whom the data of at least one post-dose efficacy indicator is collected. Only the following randomized subjects are excluded: Subjects who violates key eligibility criteria, who are not treated with the investigational drug, and who have no observed data after randomization. Per Protocol Set (PPS): A subset of the FAS, excluding subjects with significant protocol violations that may affect the primary efficacy evaluation based on the FAS. Safety Set (SS): All subjects who have used the study drug at least once. The efficacy analysis is mainly based on the FAS, but also on the PPS; the SS is used for safety analysis. **Statistical analysis method** This study will use SAS software version 9.4 or above for statistical analysis. The statistical description of quantitative indicators will calculate the number of subjects, mean, standard deviation, median, minimum and maximum (25% quantile Q1, 75% quantile Q3 where necessary), the statistical description of categorical indicators will calculate the number of subjects and percentage. The T-test or non-parametric comparison is used for inter-group comparison of quantitative indicators, and the chi-square test or Fisher's exact probability method is used for inter-group comparison of categorical indicators. **Statistical analysis and methods** Efficacy analysis Statistical analysis of the primary efficacy indicators and secondary indicators for comparison between groups is performed based on the FAS and PPS respectively. Primary efficacy indicators: The clinical cure rate of each group is counted and compared using the $\chi 2$ test or Fisher's exact probability method. Secondary efficacy indicators: fungal clearance and change in best-corrected visual acuity will be calculated based on the target eye. In addition, pain improvement and clinical effective rate will be described and compared between groups.

	Safety analysis Adverse event: Treatment-Emergent Adverse Event (TEAEs) should be focused on, i.e. treatment-emergent adverse events. The $\chi 2$ test or Fisher's exact probability method is used to compare the incidence of adverse events in each group and the incidence of adverse events related to the study drug. All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the number of cases, incidence and frequency of each type of adverse event occurring during the trial will be summarized by SOC/PT. The adverse events occurring in this trial will be tabulated and described.

Overview of study flow chart of IVIEW 1201

Visit schedule	Visit 1	Visit 2	Visit 3	Visit 4/ EOT	Visit 5/ EOS
Test stage	**Screening/Baseline/Day 1**	**Day 3**	**Day 6**	**Day 8**	**Day 14/ Early withdrawal**
Visit window period				**(± 1 days)**	**(± 1 days)**
Signing of Informed Consent Form	X				
Inclusion and exclusion criteria	X				
Randomization	X				
Demographic data[1]	X				
History taking[2]	X				
Subjective Symptoms Score[3]	X	X	X	X	X
Objective Clinical Score[4]	X	X	X	X	X
Collection of conjunctival sac secretion[5]	X	X	X	X	X
Vital signs[6]	X	X	X	X	X
Pregnancy Test[7]	X				X
Corneal endothelial cell count	X				X
Best-corrected visual acuity	X	X	X	X	X
Corneal fluorescein staining	X	X	X	X	X
Slit-lamp examination	X	X	X	X	X
Intraocular pressure measurement	X	X	X	X	X
Fundus examination	X				X
12-lead ECG examination	X				
Drug allocation[9]	X				
Study drug administration[10]	X	X	X		
Drug compliance assessment		X	X	X	
Recoding of concomitant medications	X	X	X	X	X
Adverse events[11]	X	X	X	X	X
Check of diary card		X	X	X	
Return of drugs				X	X

1.Demographic information: date of birth, gender, ethnicity, height, weight.

2.Medical history collection: including past medical history, surgical history, current medical history (time of onset, cause, etc.), comorbidities, medication history, etc. Any clinically significant examination results other than the research disease found during the screening period should be recorded as medical history.

3.Symptom scoring: Four symptoms (pain, foreign body sensation, photophobia, and tearing) were scored using a 3-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Under the guidance of the researchers, the subjects scored according to the actual situation on the day before the visit and checked in the record form.

4.Sign scoring: The three signs (conjunctival congestion, conjunctival secretion/exudation, and conjunctival edema) were scored using a 3-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe); the researchers examined and recorded them.

5. Collection of conjunctival sac secretions: Preparation before sampling: Collect bacterial culture tubes and sterile swabs provided by the central laboratory. When sampling, fully expose the bulbar conjunctiva and fornix conjunctiva, and use a sterile swab moistened with sterile 0.9% sodium chloride solution to gently swab the surface of the conjunctival sac 4 times from the inner canthus from the inside to the outside (pay attention not to miss the inner canthus, and collect the dense secretions), avoid contact with eyelashes and eyelid margins, and use eyelid openers and other instruments when necessary. After sampling, place the specimen in a sterile transport tube, mark it, and send it to the hospital laboratory for bacterial culture. All subjects need to take secretions from both eyes for bacterial culture, and indicate the subject number and eye type.

6.Vital signs: including body temperature, heart rate, blood pressure, etc.

7.Pregnancy test: For women of childbearing age, blood/urine pregnancy test can be accepted (blood pregnancy test is the main method, if it is not met, urine pregnancy test can be selected).

8.The investigators will determine whether mydriasis is required for fundus examination. If mydriasis is required, mydriasis should be applied after secretions are collected for relevant examinations. Fundus examination or fundus photography can be accepted.

9.Medication distribution: According to the medication plan, the drugs will be distributed to the subjects. These drugs will be taken by the patients themselves or with the help of caregivers or the trial team for 7 days from D1 to D7.

10.After randomization of the subjects who meet the criteria at Visit 1, the staff of the Clinical Research Center will distribute the study drugs, and then start to instruct the subjects on the topical eye drops as soon as possible and supervise the first administration. After that, the subjects will self-administer the drugs according to the dosing regimen. On the day of Visit 2 and Visit 3, the study drugs shall not be used within 1 hour before the visit.

11.Adverse events refer to all adverse medical events that occur to subjects after the first medication. However, in order to protect the rights and interests of the subjects, the recording of adverse events in this study starts from the signing of the informed consent form.

12. After completing Visit 4, IVIEW-1201 (1.0% povidone-iodine eye gel sterile solution) needs to be discontinued. If the investigator determines that treatment is still needed based on the subject's symptoms and signs, the specific treatment plan will be determined by the investigator, and the subject needs to continue in the group until Visit 5 (Day 14±1).

ABBREVIATIONS

AE	Adverse Event
TEAE	Treatment-Emergent Adverse Event
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case Report Form
D	Day
EC	Ethics Committee
EDC	Electronic Data Capture System
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Nonsteroidal Anti-inflammatory Drugs
PVP-I	Povidone Iodine
PPS	Per Protocol Set
Q1	25% quantile
Q3	75% quantile
SAE	Serious Adverse Event
SS	Safety Set
VAS	Visual Analogue Scale
BCVA	Best-corrected visual acuity
MRSA	Methicillin-resistant Staphylococcus aureus
IWRS	Interactive Web Response System
ETDRS	Early Treatment Diabetic Retinopathy Study

1. Introduction

1.1 Background

Acute conjunctivitis (also known as "pink eye") is the most common and contagious ocular infection in the United States, Asia and Europe and is a major cause of ocular morbidity, epidemic eye infections, loss of productivity and discomfort in patients. The primary causes are bacterial (mainly gram-positive and gram-negative), fungal, and viral (mainly adenovirus) infections[1]. Acute bacterial conjunctivitis can occur in people of different ages, genders, regions, and social strata.

The main clinical manifestations of acute bacterial conjunctivitis are eyelid swelling, conjunctival congestion and purulent secretions on the conjunctival surface. The secretions are mucous at first and then purulent. Acute bacterial conjunctivitis usually does not cause permanent vision loss and eye structure damage, and has obvious self-limiting properties. Even without treatment, it can be cured within 10 to 14 days.

At present, acute bacterial conjunctivitis is mainly treated with topical antibiotics and broad-spectrum antibiotics. However, due to irrational use of antibiotics in clinical practice, some pathogenic bacteria develop resistance to related antibiotics. Under such circumstances, treatment with antibiotics cannot achieve the desired therapeutic effect, and the best timing for treatment will be missed, thereby indirectly increasing the medical burden of patients.

1.2 IVIEW-1201(1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution)

1.2.1 Introduction

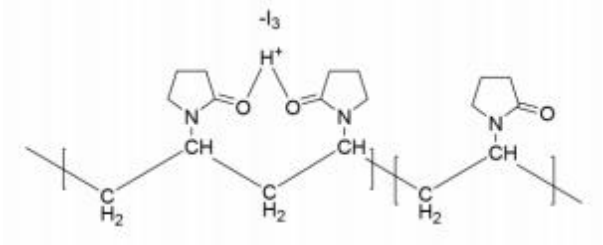
IVIEW-1201 is a brownish aqueous clear solution for ophthalmic administration, containing 1.0% (by weight) povidone-iodine for topical administration， After shaking, it becomes a brown, uniform, transparent solution. The active ingredient is povidone-iodine, whose chemical name is a complex of 1-vinyl-2-pyrrolidone homopolymer and iodine, and has in vitro antibacterial effects on a variety of bacteria, yeasts, fungi and human adenoviruses.

Povidone-iodine gradually releases iodine in the solvent and can release 1.4 to 2.4 ppm of free iodine in water. The powerful bactericidal mechanism of free iodine is to oxidize the active groups of pathogen protoplasmic proteins and combine with the amino groups of proteins to denature them, thereby effectively killing bacteria and other pathogens. It has the characteristics of low irritation, light yellowing, easy cleaning and no allergic reaction. It can quickly kill hundreds of bacteria including Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Neisseria gonorrhoeae, Candida albicans, etc.

Povidone-iodine is a commercially available iodine tincture that is routinely used in ophthalmic and general surgical procedures. A single drop of PVP-I (5% to 10%) is used as an eye disinfectant before ophthalmic surgery and is approved by the FDA for this indication. Povidone-iodine has been used for the acute and chronic treatment of a variety of human indications. Povidone-iodine solutions have been shown to be effective before eye surgery (5% PVP-I)[2,3] and before/after eye surgery (1.25% PVP-I, 2.5% PVP-I, 5% PVP-I)[4,5]. It is also effective in treating neonatal ophthalmia (2.5% PVP-I)[6,7] and acute ocular infection (1.25% PVP-I)[8]. It has been clearly demonstrated in the literature that PVP-I is, in fact, tolerated and non-toxic at concentrations below 2% (w/w)[9-11]. According to the ophthalmic literature, the active antimicrobial

drug povidone-iodine [10-14] has been shown to be well tolerated in low concentrations in animals and has low toxicity.

In a large clinical trial of 459 pediatric patients[8], povidone-iodine solution was safe and effective in the treatment of acute conjunctivitis when administered as a single dose as well as repeated doses. At the same time, it is routinely used to prevent and treat eye infections in adults[3-6] and infants[7,15]. In a placebo-controlled trial of 1.25% PVP-I in 459 children for the treatment of bacterial, viral, and chlamydial conjunctivitis, no toxicity was reported on slit-lamp examination, and no subjects dropped out due to eye drop intolerance[8]. As the PVP-I concentration decreased from 10% to 0.5%, the tolerance gradually increased and the antimicrobial efficacy also increased significantly, which is due to the balanced distribution of iodine in the aqueous solution [16]. Clinical trials of povidone-iodine (0.4% or 0.6%/dexamethasone (0.1%) eye drops in the treatment of adenoviral conjunctivitis have shown that PVP-I/dexamethasone eye drops are safe, well tolerated, and significantly promotes clinical regression and adenovirus clearance in patients with acute adenovirus conjunctivitis [17,18]. The inactive ingredients used in IVIEW-1201 (1.0% povidone-iodine ophthalmic gel sterile solution) include Gelrite® gellan gum, sodium chloride, mannitol, tromethamine, and water for injection, all of which are used in amounts below the maximum safe amount established by the FDA for use in ophthalmic preparations.



Molecular Formula:	C6H9I2NO
Molecular Weight:	364.951
CAS No.	25655-41-8

Figure 1 Chemical Structure of Povidone Iodine

1.2.2 Preclinical Study

1.2.2.1 Antibacterial Activity

The antimicrobial efficacy of IVIEW-1201 (PVP-I 0.6%) against P. aeruginosa, MRSA, and C. parapsilosis was tested at 15s, 30s, and 1min according to the protocol described in Journal of Clinical Microbiology, p635-639 (1982). The results showed that IVIEW-1201 (PVP-I 0.6%) could kill all tested pathogens at these time points.

1.2.2.2 Anti-viral Activity

In a cytopathic effect study with human AE549 cells, IVIEW-1201 (PVP-I 0.6%) demonstrated complete inactivation of Human Adenovirus Type 5 after 30 ± 5 minutes liquid-liquid contact at 37 ± 2℃.

To determine whether contact with IVIEW-1201 inactivates ("kills") virus, IVIEW-1201 was mixed directly with virus for 30 ± 5 minutes, then neutralized and the surviving virus was quantified. Neutralization controls showed that virus was effectively detected in the titer assay. Toxicity controls showed that titer plates were valid and no toxicity was observed in the 1/10 dilution of the test compound. The 70% ethanol was fully effective, and untreated virus controls were as expected. The undiluted compound IVIEW1201 (PVP-I 0.6%) was an effective virucidal, and the 1/3.2 dilution (28% after virus added) had slight virucidal activity. IVIEW1201 (PVP-I 0.6%) exhibited complete inactivation of virus.

1.2.2.3 Anti-fungal activity

IVIEW-1201 (PVP-I, 0.6%) demonstrated antimicrobial efficacy on contact with ocular isolates of Candida parapsilosis.

Following the protocol described in Journal of Clinical Microbiology, p635-639, 1982, the eradication of Pseudomona aeruginosa, MRSA and Candida Parapsilosis at 15s, 30s and 1min was measured. It showed the gel forming povidone iodine formulation IVIEW-1201 (PVP-I 0.6%) eradicated all tested pathogens at 15s, 30s and 1 minute.

1.2.3 Clinical Study

Phase II clinical study of IVIEW-1201(1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution) is currently underway for the treatment of acute adenoviral conjunctivitis. This indication was approved by the U.S. FDA on December 30th, 2018 to enter Phase II clinical trials directly, and then trials were conducted in the United States, India and China (approved on November 1st, 2019) in an international multi-center format.
Among them, the results of Indian clinical trial data showed that IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution) has good safety for human use.

1.3 IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution) Phase II Clinical Trial for the Treatment of Acute Bacterial Conjunctivitis

Comprehensive data from public literature and in vitro bacteriological evaluation tests show that IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution) is a clinical drug with great potential for the treatment of acute bacterial conjunctivitis.Therefore, we plan to conduct a multicenter, randomized, parallel-group Phase II clinical trial to evaluate the efficacy and safety of IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution) in the treatment of acute bacterial conjunctivitis, using ofloxacin eye drops as a positive control, to explore the efficacy and safety of IVIEW-1201 (1.0% Povidone Iodine Ophthalmic Gel Forming Sterile Solution) in the treatment of acute bacterial conjunctivitis and provide a basis for Phase III clinical trials.

2 . Objectives and Endpoints

2.1 Objectives

The objectives of this study are to evaluate the efficacy and safety of IVIEW-1201 in the treatment of acute bacterial conjunctivitis.

2.2 Endpoints

2.2.1 Primary Endpoints

Clinical cure rate: The proportion of subjects with a score of 0 (on a 3-point scale) for bulbar conjunctival congestion and 0 (on a 3-point scale) for conjunctival secretion/exudation at Visit 4/End of Treatment (EOT) (Day 8±1 day) and Visit 5/End of Study (EOS) (Day 14±1 day).

2.2.2 Secondary Endpoints

Clearance rate: The clearance rate of each major pathogenic bacteria at Visit 2, 3, 4 and 5: Stratified analysis shall be conducted according to the type of pathogenic bacteria and the visit time point, and the clearance rate of each kind of bacteria by the investigational drug at different times shall be calculated. Bacterial clearance is defined as positive bacterial culture at baseline and negative bacterial culture at the last visit. Bacterial clearance rate = (number of subjects cleared + number of subjects assumed to be cleared) / total number of subjects enrolled × 100%.

2.2.3 Exploratory Endpoints

Mean clinical improvement rate at Visit 2, 3, 4 and 5:

Clinical improvement rate = (pre-treatment score - post-treatment score) / pre-treatment score x 100%. The score of symptoms and signs is the sum of the scores for pain, foreign body sensation, photophobia, tearing, conjunctival congestion, conjunctival secretion/exudation and conjunctival edema.

Total effective rate (%) at Visit 2, 3, 4 and 5:

Total effective rate (%) = (number of subjects cured+ number of subjects markedly effective) / total number of subjects available for evaluation of efficacy × 100%. Comprehensive efficacy evaluation: defined as cured, markedly effective, effective and ineffective; Calculate the total effective rate; See Appendix 2: Evaluation criteria of comprehensive efficacy for judgment criteria.

3. Trial Design

3.1 Overall Design

A multi-center, randomized, parallel, positive drug-controlled study design is used. In this study, the test drug IVIEW-1201(1.0% povidone-iodine ophthalmic gel sterile solution) is selected for the test group and the positive control drug Ofloxacin Eye Drops is selected for the control group. There are a total of 120 subjects: 60 in the test group and 60 in the control group.

The subject population in this study are those aged 15 and above (inclusive) with a confirmed diagnosis of acute bacterial conjunctivitis. Subjects should complete the random allocation and initial administration of the investigational drug on the day of diagnosis.

This study will be divided into 5 visit phases, namely Visit 1 (screening/baseline period, Day 1), Visit 2 (Day 3), Visit 3 (Day 6), Visit 4/End of Treament(EOT) (Day 8 ±1 day) and Visit 5/End of Study(EOS) (Day 14±1 day).

3.2 Choice of Comparator Drug

Ofloxacin eye drops are quinolone eye drops that work by inhibiting bacterial DNA gyrase and DNA replication. Due to its unique mechanism of action, it has a broad antibacterial spectrum and strong antibacterial activity, and has a strong antibacterial effect on both Gram-negative and Gram-positive bacteria.It is effective against infections caused by sensitive species of Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pyogenes, Enterococcus, Pneumococcus, Escherichia coli, Citrobacter, Klebsiella pneumoniae, Enterobacter, Serratia, Proteus, Pseudomonas aeruginosa, Haemophilus influenzae, Acinetobacter, Campylobacter, and Chlamydia.Ofloxacin has no cross-resistance with other antibacterial drugs. It is currently widely used in the clinic to treat external eye infections such as bacterial conjunctivitis, keratitis, corneal ulcers, dacryocystitis, and postoperative infections.

After comprehensive consideration, ofloxacin eye drops produced by Santen Pharmaceutical (China) Co., Ltd. are selected as the positive control drug. In order to maintain the consistency of the medication regimen of the experimental group and the control group, the instructions are referred to determine: 1 drop/eye/time for the affected eye. The drug is administered once at the research center on the first day, and then administered once at least 3 hours apart until bedtime, with a maximum of 4 times; 4 times on the second day, with at least 3 hours between each administration; 3 times a day from the third day to the seventh day, with at least 3 hours between each administration, and the medication schedule is 7 days.

3.3 Treatment of Newly Infected Eyes

If a subject suffers from monocular disease at Visit 1 and the other healthy eye becomes infected and develops bacterial conjunctivitis after Visit 1 during the study, the newly infected eye shall be treated with the investigational drug of the subject's group, following the prescribed administration regimen for the group, i.e. "the drug shall be administered once in the study site on Day 1, and then at least once every 3 hours until bedtime, up to a maximum of 4 doses; the drug shall be administered 4 doses on Day 2, with an interval of at least 3 hours; the drug shall be administered 3 doses a day from Day 3 to Day 7, with an interval of at least 3 hours, with duration of administration of 7 days", until Visit 5. At Visit 5, if the investigator determines that the newly infected eye still requires continued treatment based on the subject's signs and symptoms, the investigator will determine the specific treatment regimen after the subject is removed from the study, but the use of IVIEW-1201 (1.0% povidone-iodine ophthalmic gel sterile solution) should be discontinued. Newly infected eyes are not included in the group test, but normal secretions are taken for bacterial culture.

3.4 Number of Subjects

This study preliminarily observed the efficacy and safety of IVIEW-1201 (1.0% povidone-iodine ophthalmic gel sterile solution) in the treatment of acute bacterial conjunctivitis, and no statistical analysis on the sample size is performed. Based on the safety evaluation requirements, 60 cases were set in the experimental group and 60 cases in the control group.

3.5 Blinding

In this study, there are significant differences between the investigational drug and the positive control drug in color, taste, properties and the patient's feeling when applying the medicine. The patient can easily distinguish them, which make it very easy to break the blind. Therefore, a single-blind or blind subject design cannot be used. The excipient components of ofloxacin placebo are unknown and too difficult to obtain for a double-blind double-simulation design. Since there are marketed drugs with clear efficacy for acute bacterial conjunctivitis, there are ethical issues in using a double-blind design with a placebo of 1.0% povidone-iodine eye gel sterile solution as a control.

The study is a blinded (assessor) study design. This means that the investigators are authorized to be blinded and non-blinded. Blinded and non-blinded team members shall be relatively independent in their work, limiting non-essential communication and avoiding disclosure of blind information.

Blindness shall be established when subjects are randomized. Blindness should be maintained until the blinded data review is completed, the database is locked and the primary statistical analysis is completed; The scope of the maintenance includes the above evaluators and blinded data analysts. The unblinding will be performed after the blinded data review is completed and the database is locked, and will be performed twice through the operation of the central randomization system. The first unblinding shall be performed after the database is locked, and the unblinding area is divided into groups X and Y and sent to the blinded data analysts for statistical analysis; The second unblinding shall be performed after the completion of the primary statistical analysis, and the specific test group or positive control drug group corresponding to groups X and Y shall be determined.

4. Selection of Subject

4.1 Inclusion Criteria

Inclusion Criteria:
Potential study subjects must meet **all** of the following inclusion criteria to be enrolled in this study.

1. Volunteered to participate in the study and signed the Informed Consent Form after receiving a verbal and written explanation of this clinical trial. In cases where the subject is unable to sign the Informed Consent Form, his/her guardian may sign in accordance with relevant regulations.
2. Aged above 15 (inclusive), male or female.
3. A diagnosis of acute bacterial conjunctivitis based on clinical observations: a) a score of ≥1 for bulbar conjunctival congestion and ≥1 for conjunctival secretion/exudation in at least one eye (same eye); and b) increased purulent, mucopurulent or mucopurulent secretions are observed in the conjunctival sac of the affected eye in all patients.
4. Willing to cooperate in the completion of all procedures and visits required for the trial.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Patients with systemic or ocular diseases, or functional disorders with comorbidities, or structural abnormalities that, in the judgment of the investigator, could adversely affect the course or results of the trial (e.g. hyperthyroidism, hepatitis, acute and chronic renal insufficiency).
2. Those who have a history of allergy or serious adverse reactions to any component of IVIEW-1201 (1.0% povidone-iodine ophthalmic gel sterile solution) and Ofloxacin Eye Drops; have a history of allergy or serious adverse reactions to quinolones; or have a cumulative total of three

or more allergies to other drugs, food and environment; or who are prone to allergic symptoms such as rash and urticaria;

3. Symptoms or signs of bacterial conjunctivitis for more than 72 hours prior to screening.
4. Suspected fungal, viral or acanthamoeba infections based on clinical observations;
5. Those with severe keratitis or corneal opacity affecting the study results;
6. Active inflammation of the cornea, iris, or anterior chamber;
7. Corrected visual acuity of less than 0.2 in either eye;
8. History of eye surgery within 3 months prior to screening;
9. Those who have a history of acute or chronic dacryocystitis;
10. Those who need to wear corneal contact lenses during the trial;
11. Those who have used antibiotic eye drops or glucocorticoid eye drops within 14 days, and oral or intravenous antibiotics within 72 hours prior to screening;
12. Systemic use of steroidal drugs within 14 days prior to screening. Local use of eye steroidal drugs or nonsteroidalanti-inflammatory drugs (NSAIDs) within 7 days before enrollment (nasally or bronchially inhaled steroidal drugs are not allowed during the study);
13. Those with co-infections requiring treatment with other anti-infective drugs in the study;
14. Those who are using other drugs that may interfere with the efficacy or safety evaluation of the drug;
15. Participation in other interventional clinical trials within 30 days prior to the study;
16. Pregnant or lactating women, women with positive pregnancy tests and those planning to become pregnant (including male subjects); subjects who do not take effective contraceptive measures within 1 month before enrollment, or subjects (including male subjects) who are unwilling to take effective contraceptive measures within the next 6 months.
17. Other conditions or illnesses judged by the clinical investigator to be unsuitable for enrollment.

4.3 Number of Cases and Allocation of Cases

There were 120 cases in total, with 60 cases in each group and 60 cases in each positive control group (ofloxacin eye drops), and they were allocated to various centers.

5. Drug Information

5.1 Investigational Drug Information

Drug Name	IVIEW-1201 (1.0% povidone-iodine ophthalmic gel sterile solution)
Specification	5g : 5mg (I2)/ bottle
Dosage Form	Eye Drops
Characteristics	It is usually a reddish brown thick liquid or gel, and after shaking it becomes a brown uniform transparent solution.
Manufacturer	Bio-Concept Laboratorie (USA)
Storage	Store in a refrigerator (2~8℃), away from light and moisture

5.2 Control Drug Information

Drug Name	Ofloxacin eye drops (Tarivid®)
Specification	5ml:15mg /bottle
Dosage Form	Eye Drops
Characteristics	Slightly yellowish green clear solution
Manufacturer	Santen Pharmaceutical (China) Co., Ltd.
Storage	Store in sealed container at 1~30℃

5.3 Package

Prior to the start of the clinical trial, all investigational drugs will be dispensed and numbered according to a randomization table. Each drug is attached with a label on its outer package. The label content includes: protocol number, drug number, blinded name of investigational drug (for clinical study use only), indication, storage, lot number, expiry date.

5.4 Study Drug Administration

IVIEW-1201
Shake well before use, 1 drop/eye/time in the affected eye. The drug shall be administered once at the study site on Day 1, and then at least once every 3 hours until bedtime, up to a maximum of 4 doses; The drug shall be administered 4 doses on Day 2, with an interval of at least 3 hours; The drug shall be administered 3 doses a day from Day 3 to Day 7, with an interval of at least 3 hours, with duration of administration of 7 days.

Ofloxacin Eye Drops (Tarivid®)
Shake well before use, 1 drop/eye/time in the affected eye. The drug shall be administered once at the study site on Day 1, and then at least once every 3 hours until bedtime, up to a maximum of 4 doses; The drug shall be administered 4 doses on Day 2, with an interval of at least 3 hours; The drug shall be administered 3 doses a day from Day 3 to Day 7, with an interval of at least 3 hours, with duration of administration of 7 days.

Administration Route
Sit or lie on back, tilt head back slightly, look up, place the test drug bottle mouth close to the eyelid of the affected eye, drop 1 drop, then gently close eyes and press the inner canthus of the eye with fingers for 1 to 2 minutes, then rest for about 5 minutes. If the test drug is not completely dropped into the eye during administration, add one drop. Among them, the test group needs to gently shake the drug solution before instilling it before use.

5.5 Prohibited Drugs or Treatments:

The Following Drugs or Treatments are Prohibited During the Study:
- Any eye medication other than the investigational drug;
- Nasally or bronchially inhaled steroidal drugs;
- Systemic use of anti-infective drugs: various antibiotics, antiviral or antifungal drugs, etc., except non-facial local treatment;
- Eye hot or cold compress;
- All types of eye surgery and treatment, including physiotherapy
- Use of corneal contact lenses.

6. Process and Indicators

This study will be divided into 5 visit phases, namely Visit 1 (screening/baseline period, Day 1), Visit 2 (Day 3), Visit 3 (Day 6), Visit 4/EOT (Day 8 ±1 day) and Visit 5/EOS (Day 14±1 day).

6.1 Study Procedures/Visit 1 (screening/baseline Day 1)

1) Signing of Informed Consent Form.
2) Demographic data: including date of birth, gender, ethnicity, height, weight.

3) Medical history collection, including past medical history, surgical history, current medical history, co-morbidity, medication history. Any clinically significant results other than the study disease found during the screening phase should be recorded as medical history.
4) Vital signs (temperature, heart rate, blood pressure).
5) Subjective Symptoms Score
6) Objective Clinical Score
7) Best-corrected visual acuity
8) Corneal fluorescein staining
9) Slit-lamp examination.
10) Intraocular pressure measurement.
11) Collection of conjunctival sac secretion
12) Fundus examination.
13) Corneal endothelial cell count.
14) 12-Lead ECG.
15) Serum Pregnancy.
16) Recording of adverse events
17) Recording of concomitant medications
18) Review of diary use/instructions

Subjects who meet the inclusion criteria and do not meet the exclusion criteria should be randomized immediately. After randomization, the drug and diary card corresponding to the randomization number are dispensed to the subjects, and the subjects will be instructed to administer the drug to the affected eye while at the site, as soon as possible.

From the start of screening to the end of screening, adverse events occurring in subjects and the use of concomitant medications and treatments must be recorded in the eCRF. Subjects who fail screening are required to have basic information and the reason for failure recorded in the subject records in detail.

6.2 Study Procedures Visit 2 (D3) and Visit 3 (Day 6) (treatment period)

Subjects will return to the study site for a visit on Day 3 and Day 6 during the treatment period and complete the following:
1) Vital signs (temperature, heart rate, blood pressure)
2) Subjective Symptoms Score
3) Objective Clinical Score
4) Best-corrected visual acuity
5) Corneal fluorescein staining
6) Slit-lamp examination
7) Intraocular pressure measurement
8) Collection of conjunctival sac secretion
9) Check of diary card and evaluation of drug compliance
10) Recording of adverse events
11) Recording of concomitant medications

6.3 Visit 4 (D8 ± 1 day) End of Treatment

Subjects will return to the study site for a visit on Day 8±1 during the treatment period and complete the following:
1) Vital signs (temperature, heart rate, blood pressure)
2) Subjective Symptoms Score
3) Objective Clinical Score

4) Best-corrected visual acuity
5) Corneal fluorescein staining
6) Slit-lamp examination
7) Intraocular pressure measurement
8) Collection of conjunctival sac secretion
9) Return of investigational drug, recovery and check of diary card, and evaluation of drug compliance.
10) Recording of adverse events
11) Recording of concomitant medications

If a subject forgets to return the investigational drugs, they can be returned at Visit 5. The treatment with the investigational drug shall be terminated at the end of this visit. If the investigator determines that continued treatment is still required (IVIEW-1201 needs to be discontinued) based on the subject's symptoms and signs, the specific treatment regimen will be determined by the investigator end recorded in the eCRF. The subject will need to remain in the study until Visit 5/EOS (Day 14±1 day).

6.4 End of Study period: Visit 5 (D14 ± 1) End of Study

Subjects will complete the following:
1) Vital signs (temperature, heart rate, blood pressure)
2) Subjective Symptoms Score
3) Objective Clinical Score
4) Best-corrected visual acuity
5) Corneal fluorescein staining
6) Slit-lamp examination
7) Intraocular pressure measurement
8) Fundus examination
9) Corneal endothelial cell count
10) Serum Pregnancy
11) Recording of adverse events
12) Recording of concomitant medications

Subjects who have not returned the investigational drugs at Visit 4 should return the investigational drugs. Subjects who withdraw early should complete the last visit in accordance with the various tests, if possible.

See Appendix 1: Symptom Scoring Criteria and Appendix 2: Evaluation criteria of comprehensive efficacyfor the specific criteria for scoring the symptoms and signs mentioned above.

6.5 Indicators

6.5.1 Indicators of clinical cure rate

6.5.1.1 Subjective Symptoms Score

- Pain: according to the subjective feelings of subjects, a 3-score scale is used (0=none, 1=mild, 2=moderate, 3=severe)
- Sensation of foreign body: according to the subjective feelings of subjects, a 3-score scale is used (0=none, 1=mild, 2=moderate, 3=severe)
- Photophobia: according to the subjective feelings of subjects, a 3-score scale is used (0=none, 1=mild, 2=moderate, 3=severe)

- Weep: according to the subjective feelings of subjects, a 3-score scale is used (0=none, 1=mild, 2=moderate, 3=severe)

See Appendix 1: Symptom Scoring Criteria for specific scoring criteria.

6.5.1.2 Objective Clinical Score:

- Scores of conjunctival hyperemia: Score the conjunctival hyperemia of the palpebral conjunctiva and bulbar conjunctiva respectively, using a 3-point scale (0= none, 1= mild, 2= moderate, 3= severe) to score the conjunctival hyperemia;
- Scores of conjunctival secretions/exudation: A 3-point scale (0= none, 1= mild, 2= moderate, 3= severe) is used to score conjunctival secretions.
- Scores of conjunctival edema: A 3-point scale (0= none, 1= mild, 2= moderate, 3= severe) is used to score conjunctival edema.

6.5.2 Other Clinical Observation Indicators

Analysis of best-corrected visual acuity, slit-lamp examination, intraocular pressure measurement, fundus examination, corneal endothelial cell count.

6.5.3 Biological sample test indicators

Collection of conjunctival sac secretions: Collect a bacterial culture tube and sterile swab from the central laboratory before sampling, and fully expose the bulbar conjunctiva and fornical conjunctiva when sampling. Use a sterile swab moistened with sterile 0.9% sodium chloride solution to gently swab the surface of the conjunctival sac 4 times starting from the inner canthus and rotating from the inside to the outside (pay attention not to missing the inner canthus, and collect the dense secretions), avoid contact with the eyelashes and eyelid margins, and use eyelid speculum and other appliances if necessary. After sampling, put the specimens into a sterile transfer tube, mark them, and send them to the laboratory department of the hospital for bacterial culture. All subjects are required to take secretions from both eyes separately for bacterial culture, with the subject number and eye type indicated.

6.5.4 Laboratory test indicators

Serum Pregnancy (female).

6.5.5 Adverse Events

Any abnormal symptoms, signs, laboratory tests or other special tests that occur during the clinical study, that are normal before treatment and abnormal clinically significant after treatment or abnormal clinically significant before treatment and worsen after treatment, regardless of its severity and whether it is related to the drug, should be recorded in detail, including the time of occurrence, clinical manifestation, severity (graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0), management process, results and the degree of correlation with the study drug (definitely related, probably related, possibly related, possibly unrelated, definitely unrelated), and followed up until return to normal or baseline level or the investigator can give a reasonable explanation for the abnormality and believes that follow-up is not necessary. Those that are definitely related, probably related, possibly related are classified as adverse reactions.

In this study, the following abnormal laboratory values that were considered clinically significant were not treated as adverse events:

Abnormal laboratory test values with clinical significance that existed before enrollment, for example, the subject may have other systemic diseases, but no significant clinically significant changes occurred during the study will not be considered adverse events.

7. Assessment of Efficacy

7.1 Clinical Efficacy Assessment

Clinical cure rate: The proportion of subjects with a score of 0 (on a 3-point scale) for bulbar conjunctival congestion and 0 (on a 3-point scale) for conjunctival secretion/exudation at Visit 4/End of Treatment (EOT) (Day 8±1 day) and Visit 5/End of Study (EOS) (Day 14±1 day).

Clinical improvement rate = (pre-treatment score - post-treatment score) / pre-treatment score x 100%. The score of symptoms and signs is the sum of the scores for pain, foreign body sensation, photophobia, tearing, conjunctival congestion, conjunctival secretion/exudation and conjunctival edema.

Total effective rate (%) = (number of subjects cured+ number of subjects markedly effective) / total number of subjects available for evaluation of efficacy × 100%. Comprehensive efficacy evaluation: defined as cured, markedly effective, effective and ineffective; Calculate the total effective rate; See Appendix 2: Evaluation criteria of comprehensive efficacy for judgment criteria.

7.2 Biological Sample Test Indicators

7.2.1 Bacterial clearance rate

Bacterial clearance is defined as positive bacterial culture at baseline and negative bacterial culture at the last visit.

Bacterial clearance rate = (number of subjects cleared + number of subjects assumed to be cleared) / total number of subjects enrolled × 100%.

For the clearance rate of each major pathogenic bacteria, stratified analysis shall be conducted according to the type of pathogenic bacteria and the visit time point, and the clearance rate of each kind of bacteria by the investigational drug at different times shall be calculated.

The specific judgment criteria are as follows:

Clearance: No pathogenic bacteria of the original infection are cultured in the specimen culture from the original infection site after treatment;

Assumed clearance: Bacteriological results are considered assumed clearance in certain diseases where the disappearance of signs and symptoms makes culturable materials unavailable or the method of obtaining specimens is too invasive for recovered patients;

Not cleared: The pathogenic bacteria of the original infection are still cultured in the specimen culture from the original infection site after treatment;

Assumed not cleared: For patients judged to be clinically ineffective, if the culture has not been done or is unlikely to be done, the pathogenic bacteria can be assumed not cleared;

Partial clearance: At least one of the multiple pathogenic bacteria isolated at the original infection site is cleared at the end of treatment;

Replaced: Those whose bacterial culture results 1 week after treatment show negative results for the original pathogen bacteria and the appearance of new pathogen bacteria, but with no relevant symptoms and signs observed;

Re-infected: Those whose bacterial culture results 1 week after treatment show negative results for the original pathogen bacteria, but with new pathogenic bacteria appearing and signs and symptoms related to re-infection.

7.2.2 Evaluation of specific etiological efficacy

(1) Bacterial culture positivity rate = the number of positive bacterial culture as a percentage of the total number of cases in the study.

(2) Bacterial species clearance rate = the total number of bacterial species cleared as a percentage of the total number of pathogenic species isolated at the end of treatment.

(3) Negative conversion rate of bacterial culture = The percentage of patients whose bacterial culture turns negative after treatment among those with positive bacterial culture before treatment.

(4) Stratified evaluation of pathogens

① Analysis of 120 patients at the end of all studies

Pathogen/Number of patients	Cleared	Not cleared	Replaced	Re-infected
Staphylococcus aureus				
Streptococcus pneumoniae				
Haemophilus influenza				
Corynebacterium				
Streptococcus hemolyticus				

② Observation of different pathogens for different duration of administration

Duration of administration / Number of patients	Staphylococcus aureus	Streptococcus pneumoniae	Haemophilus influenza	Corynebacterium	Streptococcus hemolyticus
Baseline					
Visit 2					
Visit 3					
Visit 4					
Visit 5					

8. Compliance

Compliance will be determined by subject self-report as recorded in subject diaries. Missing diary data may be collected by subject questioning. There will also be drug dispensing and return logs to be completed by the investigative site.

% = actual number of medication times / theoretical number of medication times × 100%.

A calculated result less than 80% or greater than 120% was considered to be poor compliance

9. Assessment of Safety

9.1 Adverse Events (AE)

"Adverse Event" (AE) is any adverse medical event that occurs after administration of investigational drug and may manifest itself as a symptom, sign, disease or abnormal laboratory test, but is not necessarily causally related to the investigational drug.

AEs in this trial are collected from the time of the first dose of study drug to the completion of the last visit or trial process planned in the protocol. However, for the protection of subjects' rights, the recording of adverse events in this study starts with the signing of Informed Consent Form. The incidence of adverse events in this trial is calculated based on adverse events that occur after the first dose. However, the following conditions should not be recorded as AEs:

- Pre-existing conditions identified at screening (for example, laboratory tests, vital signs, etc. show clinically significant abnormalities at screening that, in the judgment of the investigator, exist prior to the subject's informed consent); such conditions should be recorded as medical history/concomitant disease.

- Medical and surgical examination process (such as liver biopsy, endoscopy); however, the diseases that cause these tests may be adverse events.

- Existing concomitant diseases or pre-existing signs and symptoms at screening have progressed as expected, but have not worsened.

The sources of adverse events include:

- Subject's responses to questions about his/her health status (non-leading questions at each visit such as "How are you feeling since your last visit") .

- Symptoms spontaneously reported by the subject.

- Changes or abnormal findings or examinations that are assessed by the investigator to be clinically significant.

- Other information related to the health of the subject that is made known to the investigator (e.g. hospitalization).

9.2 Serious Adverse Events (SAE)

Each AE is to be classified by the Investigator as SERIOUS or NON-SERIOUS.
An SAE is generally an adverse event that results in any one or more of the following outcomes, including:

- Leading to death.
- Life-threatening (It refers to the immediate risk of death, not the death that may occur in the future when the disease progresses).
- Leading to hospitalization or prolonged hospitalization; this does not include elective surgery or prolonged hospitalization or prolonged hospitalization due to non-adverse events.

- Leading to permanent or significant loss of function.
- Congenital anomaly/birth defects
- Other medically important events: They may not be immediately life-threatening, lead to death or hospitalization, but are also usually considered serious if medical measures are required to prevent one of the above. Examples include important treatment in the emergency room or allergic bronchospasm at home, cachexia or convulsions requiring no hospitalization, development of drug dependence or addiction.

9.3 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) refers to a serious adverse reaction whose nature or severity is beyond the information available in the investigator's brochure of the test drug, the package insert of the marketed drug or the summary of product characteristics.

The sponsor will promptly report SUSARs to all investigators and clinical study sites participating in the clinical trial; the sponsor will report any known SUSARs to the drug regulatory agency and the health administrative department as required.

9.4 Assessment of Adverse Event Correlation

The correlation between the adverse event and the study drug is assessed by the investigator according to the following:

☆ Definitely related to the study drug

There is evidence of taking the study drug; the occurrence of adverse events and the time sequence of taking the study drug are reliable; the occurrence of adverse events is explained more reasonably by the study drug than by other reasons; the withdrawal reaction is positive; the repeated drug use test is positive; the pattern of adverse events is consistent with previous understanding of this drug or this type of drug.

☆ Probably related to the study drug

There is evidence of taking the study drug; the occurrence of adverse events and the time sequence of taking the study drug are reliable; the occurrence of adverse events is explained more reasonably by the study drug than by other reasons; the withdrawal reaction is positive.

☆ Possibly related to the study drug

There is evidence of taking the study drug; the occurrence of adverse events and the time sequence of taking the study drug are reliable; adverse events may be caused by the study drug or by other reasons; the withdrawal reaction is positive.

☆ Possibly unrelated to the study drug

There is evidence of taking the study drug; adverse events are more likely to be caused by other reasons; the withdrawal reaction is negative or ambiguous; the repeated drug use test is negative or ambiguous.

☆ Definitely unrelated to the study drug

The subject does not take the study drug; or the occurrence of adverse events and the time sequence of taking the study drug are not reliable; or there are other significant reasons that lead to adverse events.

9.5 Severity of Adverse Events

The investigators will categorize the severity of each adverse event by describing the clinical symptoms with reference to the five-grade judgment criteria developed by NCI CTCAE V5.0. The severity classification is as follows.

- Grade 1: mild, asymptomatic or slight; only seen in clinical practice or diagnosis; no treatment is required;
- Grade 2: minor, local, or non-invasive treatment is required; age-appropriate instrumental activities of daily living are limited*;
- Grade 3: Serious or medically significant but not immediately life-threatening; leading to hospitalization or prolonged hospitalization; disabling; self care activities of daily living are limited**;
- Grade 4: life-threatening, requiring emergency treatment;
- Grade 5: AE-related deaths.

*Instrumental activities of daily living refer to cooking, shopping for clothes, telephone use, money management, etc.

**Self care activities of daily living refer to bathing, dressing and undressing, eating, washing hands and face, taking medication, etc., in a non-bedridden state.

9.6 Recording of Adverse Event

Any adverse event, whether serious or not, and whether or not related to the study drug, must be recorded on the case report form. Patients who withdraw due to any adverse event should be followed up by the investigator until recovery or stabilization, or until baseline levels are reached, or until clinical manifestions is judged by the investigator to be basically stable that require no further follow-up, and should be recorded in the original document. Follow up can be divided into hospitalization, outpatient, home visit, telephone, communication and other forms according to the severity of adverse events.

9.7 Name of Adverse Event

The name of an adverse event should be a medical term and a medical diagnosis should be used in preference. That is, if multiple symptoms, signs and abnormal laboratory values can be described or attributed to the manifestation of a disease or impairment, this is treated as an adverse event. If a definitive diagnosis cannot be made, symptoms/signs should be used. When the later diagnosis is clear, the record is updated to replace the previous signs/symptoms with the diagnosis.

9.8 Start and End Time of the Adverse Event

The onset time of the AE is the time when the subject first experiences the AE or related symptoms and signs, not the time reported by the subject or the time when the investigator is informed. If the AE is a clinically significant abnormal laboratory test or auxiliary examination, the onset time is recorded as the sampling or examination time.

The end time of the AE is the date when the AE or AE-related symptoms and signs cease. If the AE is a clinically significant abnormal laboratory test or auxiliary examination, the end time is the sampling or examination time.

If the same AE occurred two or more times in the same subject and the subject recovered between the two events, it is counted as two AEs.

The severity of the AE increased without adding an additional AE record.

The SAE report needs to provide:
1) Time of event occurrence (first symptom or laboratory test abnormality);
2) Time when the event reaches the SAE severity standard;
3) Time when the event ends.

9.9 Outcome of adverse events

The researchers followed up the subjects' adverse events and filled in the adverse event outcomes/results, including recovery, recovery with sequelae, improved, not improved, died, and unknown.

9.10 Reporting Process of Serious Adverse Events

Serious adverse events occurring during the clinical trial, whether or not related to the study drug, must be reported immediately to the sponsor by the investigator, who must complete an adverse event attached table and notify the sponsor and the contract research organization within 24 hours. The investigator should then provide a detailed, written follow-up report in a timely manner, which should adhere to the 24-hour time limit and the reporting process described above. The investigator should also report to the research institution, ethics committee, etc. of this site as required by the study site.

In the event that the sponsor and the investigator cannot agree on the causal relationship between the adverse event and the drug, expedited reporting should also be conducted if either party determines that a correlation with the trial drug cannot be excluded. Therefore, the sponsor requires to provide supporting documents of serious adverse events (such as attached table of adverse events, checklist), and the study site should assist in submitting information to the sponsor as soon as possible.

For the reporting of death events, the investigator should provide the sponsor and the Ethics Committee with required data, such as autopsy report and final medical report. For fatal or life-threatening SAE events, the investigator should report the follow-up report and complete the follow-up information within 7 days of the initial report whenever possible.

The investigator is the first responsible person for the collection and follow-up of adverse events/serious adverse events and should follow up until the event is over, the condition is stable, a reasonable explanation has been given, loss to follow-up or death; the investigator should timely provide follow-up information as requested by the sponsor, and ensure the accuracy and consistency of the report content.

The investigator should sign for and read the safety information of the clinical trial provided by the sponsor in a timely manner, and consider whether the subject’s treatment should be adjusted accordingly. If necessary, the investigator should communicate with the subject as early as possible and report SUSARs provided by the sponsor to the Ethics Committee.

9.11 Pregnancy

The investigator should inform the subjects that any pregnancy that occurs during the study and within 6 months after the completion of the study must be reported to the investigator.Pregnancy is not an adverse event, but if the investigator learns that the subject or her spouse is pregnant, it must be reported to the principal investigator, ethics committee, contract research organization and sponsor of the center within 24 hours.

Researchers should advise subjects and discuss the risks of continuing pregnancy and possible effects on the fetus. Female subjects should be advised to stop taking the drug. Subjects should continue to be followed up until 1 month after termination of pregnancy or delivery.

Pregnancy in the partner of a male subject during the study should also be reported to the investigator and sponsor. Partners of patients should also be advised and followed as described above.

10. Data Management and Statistical Analysis

An independent third party will be responsible for data management and biostatistics, participate in trial design and program implementation, be responsible for clinical data management and statistical analysis, and complete data management reports and statistical analysis reports.

10.1 Randomization

Approximately 120 patients will be randomized in a 1:1 ratio to either IVIEW-1201 or positive control drug. This trial adopts a randomized block method to randomly assign subjects, using a central randomization system. The Interactive Web Response System (IWRS) will be used for the allocation of randomization numbers and the drugs will be dispensed according to the drug numbers assigned by the IWRS. The drug number will be recorded in the subject's eCRF. There is competition for enrollment among the study sites participating in this study. The investigators at each study site should log into the system after screening all eligible subjects and fill in the screening information, so that the subjects can be randomized and obtain a randomization number.

The authorized investigator will obtain a randomization number of each randomly assigned patient through the randomization system, prompting the results of the random treatment allocation. And obtain the corresponding drug number.

10.2 Data Management

10.2.1 Original Data and Original Documents

Original data
Original data is all the information in the original records generated by clinical findings, observations or other activities in the trial and their qualified copies, which are necessary for the restoration and evaluation of the trial. Original data is included in the original record.

Original record
Original records are the earliest documents, data and records (e.g. hospital records, clinical and office charts, laboratory records, memoranda, subject diaries or evaluation forms, drug dispensing records, data recorded by automated instruments, qualified copies or duplicates that have been verified as accurate copies, microfilm, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept by pharmacies, laboratories and pharmaceutical technical departments participating in clinical trials).

Clinical trial specific original data
The investigator must keep the records of the subjects.

The subject’s medical history results and other clinically relevant outcomes, demographic data and AEs should be recorded in specific original records and then transcribed into the Case Report Form (CRF) for each subject. Laboratory results will be transcribed into the CRF by the investigator and labeled as normal,

abnormal not clinically significant or abnormal clinically significant. If necessary, specific exceptions will be described in detail in the CRF.

CRF

This trial uses an electronic case report form, the content of which is collected by the researcher or his/her authorized personnel through the clinical electronic data collection and management system.

1) All subjects who have signed the informed consent form must fill in the case report form in accordance with the instructions, and record any items in the case report form carefully and in detail;
2) All data in the case report form must be checked with the subject's original document data to ensure accuracy;
3) Data that are significantly higher or outside the clinically accepted range must be verified and, if necessary, judged by the researcher;
4) For other details, please refer to the electronic case report form filling guide.

After the completed electronic case report form is reviewed by the clinical monitor, the data manager will conduct data verification and management. After data collection and cleaning are completed, the researcher will sign and confirm online.

The original subject file is the original record of the subject kept by the trial unit. The trial data must be entered into the CRF in a timely manner.

The completed CRF is the exclusive property of the sponsor and cannot be provided to a third party in any form without the sponsor's written permission, except for the authorized representative of the relevant regulatory agency or ethics committee (EC).

10.2.2 Data management process

1) This study adopts an electronic data management system. Construction of electronic CRF: The data administrator constructs the electronic CRF (eCRF) according to the study protocol.

2) Permission allocation: The data administrator creates separate accounts and grants different permissions according to the different identities (e.g. data entry staff, investigator, CRO). The data entry person has the permission to enter, modify, question and feedback data; the principal investigator has the permission to modify, browse, question feedback and sign electronically; the CRO has the permission to browse and send queries; the data administrator has the permission to browse, send queries and lock data.

3) Data entry: The clinical investigator or a data entry person (clinical coordinator) appointed by the investigator enters data from the study medical record into the eCRF in a timely and accurate manner. For external data, the appropriate protocols for external data transfer need to be developed during the operation of the project. At least 2 transfers should be made before the database is locked in order to confirm the accuracy of external data. After the database is locked, the data is needed to be transferred to the statistical analysis unit according to the external data transfer protocol.

4) Sending and resolution of queries: The CRO, the data administrator, the CRO send all queries through the EDC system, and the data entry person or the investigator answers the questions and correct incorrect data. Queries can be sent repeatedly if necessary and all records are kept in the eCRF.

5) Modification and review of data: Data can be modified by the data entry person or the investigator after verifying the data, and the reasons for the modifications need to be filled in on the eCRF. The investigator has the permission to sign all final data electronically.

6) Data locking and export: After all data has been verified for accuracy, the data administrator locks the data. Any modifications required after the data has been locked need to be signed off by the sponsor, investigator, data entry person, CRO and data administrator before implementation. All data is eventually exported by the data administrator and handed over to the statistician for analysis.

10.3 Statistical Analysis

10.3.1 Selection of statistical analysis data set

1) Full Analysis Set (FAS): All subjects randomized and for whom the data of at least one post-dose efficacy indicator is collected. Only the following randomized subjects are excluded: Subjects who violates key eligibility criteria, who are not treated with the investigational drug, and who have no observed data after randomization.

2) Per Protocol Set (PPS): A subset of the FAS, excluding subjects with significant protocol violations that may affect the primary efficacy evaluation based on the FAS.

3) Safety Set (SS): All subjects who have used the study drug at least once.

The efficacy analysis is mainly based on the FAS, but also on the PPS; the SS is used for safety analysis.

10.3.2 Statistical analysis method

This study will use SAS software version 9.4 or above for statistical analysis.

The statistical description of quantitative indicators will calculate the number of subjects, mean, standard deviation, median, minimum and maximum (25% quantile Q1, 75% quantile Q3 where necessary), the statistical description of categorical indicators will calculate the number of subjects and percentage.

The T-test or non-parametric comparison is used for inter-group comparison of quantitative indicators, and the chi-square test or Fisher's exact probability method is used for inter-group comparison of categorical indicators.

10.3.3 Missing value imputation

For primary efficacy indicators, missing data are imputed using appropriate methods. If applicable, data from the last observation before dropout may be used to impute (LOCF method), and other missing value imputation methods should be explored for sensitivity analysis.

10.3.4 Statistical analysis and methods

- Subject disposition

All enrolled, dropped, eliminated and completed subjects at each study site are listed to compare the compliance of each group.

- Demographic data

A baseline analysis is performed on the demographic and related characteristics of enrolled subjects in each group to investigate the comparability among groups.

- Efficacy analysis

Statistical analysis of the primary efficacy indicators and secondary indicators for comparison between groups is performed based on the FAS and PPS respectively.

Primary efficacy indicators: The clinical cure rate of each group is counted and compared using the χ^2 test or Fisher's exact probability method.

Secondary efficacy indicators: fungal clearance and change in best-corrected visual acuity will be calculated based on the target eye. In addition, pain improvement and clinical effective rate will be described and compared between groups.

- Safety analysis

Adverse event: Treatment-Emergent Adverse Event (TEAEs) should be focused on, i.e. treatment-emergent adverse events. The χ^2 test or Fisher's exact probability method is used to compare the incidence of adverse events in each group and the incidence of adverse events related to the study drug. All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the number of cases, incidence and frequency of each type of adverse event occurring during the trial will be summarized by SOC/PT. The adverse events occurring in this trial will be tabulated and described.

Ocular and systemic signs and symptoms, ECG and other indicators: Descriptive statistics of ocular and systemic signs and symptoms, ECG and other indicators is performed by visit. Clinically significant changes in relevant examinations in subjects before and after treatment are described, with special attention given to the occurrence of abnormal clinically significant conditions following drug administration in subjects who are normal or abnormal not clinically significant before treatment.

See the Statistical Analysis Plan for the statistical analysis methods of other indicators.

11. Trial Management

11.1 Subject Withdrawal Criteria

Subjects will be removed from the study for the following reasons:

1) Death;
2) Allergy or intolerance to the study drug;
3) Pregnancy events during the course of the study;
4) Self-withdrawal by the subject/guardian;
5) Subject is lost to follow-up;
6) Adverse events occurring in subjects that, in the judgment of the investigator, will adversely affect the subject during the continued treatment period;
7) Serious violation of the protocol by the subject which, in the judgment of the investigator, affects the evaluation of the trial results;
8) Other reasons for subject withdrawal in the judgment of the investigator.

11.2 Trial Termination

1) The National Medical Products Administration requires the trial to be terminated;
2) The Ethics Committee requires the trial to be terminated;
3) The sponsor requires the trial to be terminated.

11.3 Ethics

This study will follow the Declaration of Helsinki and comply with ICH guidelines, GCP and other relevant regulations. This study will be carried out in strict accordance with the trial protocol. The protocol and Informed Consent Form and any modifications must be approved by the Ethics Committee prior to implementation. The rights, safety and health of the subjects are given priority over scientific and social interests. Prior to the start of the trial, the investigator should provide the subject with an Informed Consent Form and explain detailed information about the study to the subject in easy-to-understand language. The investigator should give the subject necessary time to understand the details about the study before the Informed Consent Form is signed and dated by the subject himself/herself or his/her guardian and the investigator.

11.4 Quality Control and Quality Assurance of Trials

This clinical trial is a multi-center clinical trial, and the trial task is jointly undertaken by several national drug clinical trial institutions. All researchers should have the professional expertise, qualifications and capabilities to undertake this clinical trial, and undergo GCP-related training. Each center conducts clinical trials at the same time, manages the trial drugs with the same procedures, trains researchers participating in the trial according to the same trial protocol, establishes standardized methods for efficacy and safety evaluation, and has unified quality control for clinical evaluation methods in each center. The research leader of each trial unit should hold a meeting of researchers to learn the trial protocol, unify standards, and unify understanding before implementing clinical research work in a division of labor.

During the clinical trial, the principal investigator audits the trials of each center according to the requirements of NMPA, and the monitor regularly monitors the progress and quality of the trial, verifies the data, and performs necessary coordination work. At the end of the trial, the clinical research leader unit and the sponsor organize a summary meeting to complete the clinical research summary report in a timely manner.

11.5 Study Drug Handling

The sponsor is responsible for printing the forms in the research plan, providing qualified trial drugs free of charge, and working with the clinical research unit to complete:

1) Records of the use of trial drugs, including quantity, transportation, acceptance, distribution, application and recovery;
2) The use of trial drugs is the responsibility of the researcher, and the drugs are distributed according to random sequence numbers. All trial drugs are only used for the subjects of the trial;
3) All remaining trial drugs are returned to the sponsor and recorded;
4) The dosage and usage of drugs comply with the provisions of the trial plan;
5) The sponsor must have appropriate packaging and labels for all drugs used in clinical trials, and indicate that they are for clinical trials only;
6) The monitor monitors the supply, use, storage and handling of remaining trial drugs.

11.6 Data Retention

According to GCP guidelines, researchers/clinical trial institutions must keep all CRFs, original documents supporting data collected from each subject, and all research documents required by GCP and current regulations. Researchers/clinical trial institutions must take measures to prevent these documents from being accidentally or prematurely destroyed. The above documents must be kept for at least 5 years after the end of this trial.

If the sponsor or drug regulatory agency needs to review information related to this study, the researcher must provide this information.

11.7 Duties

The sponsor, investigator, research responsible unit and participating research unit must strictly abide by the "Good Clinical Practice for Drugs" and the provisions of this plan and assume corresponding responsibilities.

11.8 Protocol Amendment

The principal investigator leads the study, and the participating institutions and the sponsor jointly develop the plan through a plan discussion meeting. After the ethics committee of the lead institution reviews and approves the plan, in principle, the plan will not be changed. If it is found during the trial that the plan needs to be modified, it must be submitted to the ethics committee of the lead institution for approval before implementation. Under this item, the revision content should be recorded in detail, the plan version should be updated, and the plan should be submitted to each center for ethical filing/review.

12. Publication

After the trial is completed, and after obtaining the written consent of the sponsor, the research unit can publish the research results of this clinical trial in the form of a paper, but the source of the drug must be stated, and the researchers of each research unit have the right to sign the paper. The sponsor can also publish the paper or use the trial content, or participate in the signing as needed.

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14. Appendix

Appendix 1: Symptom Scoring Criteria

(1) Eye pain

Visual analogue scale (VAS), using a vernier scale with values from 0 to 10 on which the subject indicates the location of their pain degree. The score is determined by location. The higher the score, the more intense the pain degree.
It will be scored for ocular comfort (Scale 0 for no pain; 10 for the most severe pain) Calculate the improvement rate based on the scale difference.
0 No pain
1 1 - 3
2 4 - 6
3 7 - 10

(2) Sensation of foreign body
0 No sensation of foreign body
1 Mild sand-like sensation
2 Moderate sand-like sensation
3 Intolerable

(3) Photophobia
0 No photophobia
1 Discomfort in the presence of light
2 Reluctant to open eyes in the presence of light
3 Unable to open eyes in the presence of light

(4) Tears
0 No tears
1 A few tears
2 Significant tears
3 Constant tears

Appendix 2: Evaluation criteria of comprehensive efficacy

Cured: ≥ 90% reduction in Scores of subjective symptoms and Objective Clinical Score

Markedly effective: ≥70% but <90% reduction in Scores of subjective symptoms and Objective Clinical Score

Effective: ≥30% but <70% reduction in Scores of subjective symptoms and Objective Clinical Score

Ineffective: <30% reduction in Scores of subjective symptoms and Objective Clinical Score