

Supplementary Materials

Pharmacokinetics, safety, and immunogenicity of intravenous and subcutaneous single-dose of QX002N injection in healthy subjects: A randomized, open, parallel, single-center, phase I study

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Summary of Clinical Study Protocol

Research topic

A randomized, open-label, parallel, single-dose, single-center, phase I clinical study to evaluate the pharmacokinetic profile, safety and immunogenicity of subcutaneous and intravenous infusion QX002N injection in healthy subjects

drug name

QX002N injection

Indications

Intended for the treatment of ankylosing spondylitis

Stage of the trial

Phase I

Scheme number

QX002NA-04

Applicant company

Jiangsu Qyuns Therapeutics Co., Ltd, Taizhou, Jiangsu 225300, China

Clinical unit

Shulan (Hangzhou) Hospital

Research Purpose

Main purpose: To evaluate the pharmacokinetic profile of a single subcutaneous injection and intravenous infusion of QX002N in healthy subjects, and to investigate the absolute bioavailability of subcutaneous injection of QX002N compared to intravenous infusion of QX002N.

Secondary objectives: To evaluate the safety of a single subcutaneous injection and intravenous infusion of QX002N in healthy subjects, and to evaluate the immunogenicity of a single subcutaneous injection and intravenous infusion of QX002N in healthy subjects.

Planned enrollment

24 healthy subjects are planned to be enrolled.

Research design and process

This trial is a randomized, open-label, parallel, single-dose, single-center, phase 1 clinical study. It is planned to enroll 24 healthy subjects, 12 cases in each group.

Screening period(D-14-D-1): Subjects were evaluated for various tests and inclusion exclusion criteria.

Baseline period(D-1): Subjects eligible for enrollment were randomly assigned in a 1:1 ratio to either the QX002N 240mg SC group or the QX002N 240mg IV group and were admitted to the clinical trial center.

Observation period(D1-D6): Participants were administered with a 240 mg dose of QX002N either via a single subcutaneous injection or an intravenous drip on D1. Safety assessments, PK blood collection, and ADA blood collection were conducted during the monitoring period. They were discharged on D6.

Follow-up period(D8-D127): The participants were monitored until Day 8. Safety evaluation, blood collection for pharmacokinetic analysis, and blood collection for anti-drug antibody testing were carried out during each visit. This continued until the completion of the 127-day study.

Experimental drug

QX002N injection is a sterile water injection form, with a specification of 100mg (1mL)/bottle,

which is produced and provided by Jiangsu Cellularforce Biotechnology Co., Ltd.

Dosage regimen

Dose group 1: QX002N 240 mg SC group, single administration, administration volume of 2.4 mL. Please be aware that this group uses a non-injection skin administration method, targeting the area outside a 5cm circumference. Moreover, injections can be administered at various positions. Prior to the injection, it is essential to disinfect the injection site and assess the skin condition to prevent induration, scarring, redness, and swelling.

Dose group 2: QX002N 240 mg IV group, single administration, administration volume of 2.4 mL. Please be aware that this particular dose should be administered via intravenous infusion, with a minimum infusion time of 1 hour, and should not be rapidly administered as an intravenous bolus.

Combination medication/therapy

Administration of live vaccines or live attenuated vaccines is not allowed during the study.

Any concomitant medication other than the one used to manage adverse events is generally prohibited during the trial. Any concomitant medication used during the trial besides the investigational drug should be meticulously documented in the case report form, specifying the drug name, dosage, administration route, date of administration, and indication for use, among other details.

Screening test program and time

Screening tests were performed on days -14 to -2.

Screening tests include: demographic information (age, gender, ethnicity), medical history (past medical history, history of trauma/surgery), history of smoking and alcohol consumption, history of allergies, history of recent medication use; height, weight, and calculation of BMI; vital signs (pulse, respiration, blood pressure, temperature); physical examination 12-lead electrocardiogram; clinical laboratory tests (blood biochemistry, blood counts, urinalysis, and coagulation counts); blood pregnancy test (women of childbearing age only); chest radiograph; thyroid function; abdominal ultrasound (liver, gallbladder, pancreas, spleen, both kidneys); T-cell test for tuberculosis infection (TSPOT); infectious disease tests (Hepatitis B surface antigen qualitative [HBsAg], Hepatitis C virus antibody [Anti-HCV], Hepatitis C virus core antigen [HCV-cAg], Human Immunodeficiency Virus (HIV) antigen); anti-HIV test; syphilis helminth test; and other tests. Anti-HIV Combined Test, Syphilis Spirochete Specific Antibody Assay [TP-ELISA]); Humoral Immunoassay (Anti-Nuclear Antibody [ANA], Anti-Double-stranded DNA [anti-dsDNA]).

(During the epidemic period, subjects may be subjected to new crown nucleic acid testing and chest CT examination according to the requirements of the hospital, and if the chest CT examination is performed before admission, the anteroposterior chest X-ray examination will not be performed during the screening period.) Depending on the epidemic situation, the relevant inspections may be adjusted.)

Check-in (baseline) check item and time

The baseline examination was conducted on the 4th day, and the examination items included: 1. Vital signs (pulse, respiration, blood pressure, body temperature); 2. Physical examination; 3. 12-lead electrocardiogram; 4. Clinical laboratory tests (blood biochemistry, blood routine), urine routine, coagulation routine); 5. Blood pregnancy test (only for women of childbearing age); 6. Urine drug screening; 7. Alcohol Breath Test.

Inclusion criteria

Only those who meet all the inclusion criteria can be enrolled: 1. Healthy adults aged 18~50 years old (including both ends) at the time of signing the informed consent form; 2. Male subjects weigh ≤ 50.0 kg, female subjects weigh ≤ 45.0 kg, and both ≤ 100.0 kg; body mass index is in the range of 18.0-28.0 kg/m²; 3. After comprehensive examination, including vital signs, physical examination, laboratory tests, 12-lead ECG, Abdominal ultrasound and anteroposterior chest x-ray examination, all the results were normal or abnormal but not clinically significant; 4. Agree to have no fertility plan during the trial and within 6 months after the end of the trial and voluntarily take effective contraceptive measures; 5. The subject fully understands the purpose, nature, method and possible adverse reactions of the trial, voluntarily acts as a subject, and signs the informed consent form; 6. Able to complete the test according to the requirements of the protocol.

Exclusion criteria

Those who meet the following 1 exclusion criteria are excluded: 1. Those who have received monoclonal antibodies targeting IL-17 in the past; 2. Those who are allergic to two or more drugs or food, or who may be allergic to the study drug or any component of the study drug as judged by the investigator; 3. Those who have a history of drug abuse within five years prior to screening or who have used drugs in the 3 months before the trial, or those who have a positive urine drug abuse screen; 4. Those who have one or more positive tests for Hepatitis B surface antigen (HBsAg), hepatitis C antibody (IgG), hepatitis C virus core antigen, human immunodeficiency virus (HIV) antibody and Treponema pallidum specific antibody (TP-Ab); 5. Individuals who have had infections, such as chronic or local infections, within the 7 days preceding the screening, those with a history of recurring infections and underlying conditions that make them susceptible to infections, as well as those with a history of recurrent (more than once) or widespread herpes zoster infection, and a history of opportunistic infections; 6. Those with a history of active tuberculosis, or those with active or latent tuberculosis infection at the time of screening; 7. Clinical significance can be found in abnormal laboratory test results or in the presence of various diseases such as gastrointestinal, eye, kidney, liver, lung, nerve, blood, endocrine, tumor, immune, metabolic, gynecological (for women of childbearing age only), mental, cardiovascular, and cerebrovascular diseases, etc., within the 6 months prior to screening; 8. Individuals who have given at least 400 mL of blood, experienced a loss of at least 400 mL of blood within 4 weeks before screening, or undergone a blood transfusion within 8 weeks before screening; 9. Individuals who have been inoculated with live (weakened) vaccines up to 4 weeks prior to the screening process or those intending to take live (weakened) vaccines during the trial are included. 10. Individuals who have taken prescription medication or Chinese herbal remedies in the 4 weeks leading up to screening, or who have used over-the-counter medications or nutritional supplements (such as vitamins, calcium supplements, etc.) within 2 weeks prior to screening, are not eligible to participate. 11. Smoking more than 5 cigarettes per day or habitually using nicotine-containing products within 3 months before screening; 12. Drinking more than 14 units of alcohol per week within 6 months before screening (1 unit alcohol = 360 mL of beer or 45 mL of 40% alcohol or 150 mL of grape sprinkles) or those who have taken alcohol-containing products 2 days before dosing; 13. Those who have participated in clinical trials of any drug or medical device within 3 months or 5 half-mourning periods (whichever is longer) before screening; 14. Female subjects who test positive for pregnancy or are lactating; 15. Any additional circumstances that the researcher believes could impact the subject's capacity to give informed consent or adhere to the trial protocol, as well as any factors influencing the subject's involvement in the trial that might impact the trial results or their own safety.

Exit criteria

The researcher has decided to withdraw from the study due to several reasons: The researcher considers it necessary to stop the trial from the perspective of medical ethics; the subject is pregnant; a serious adverse event (SAE) occurs, and it is not appropriate to continue to accept the trial; the researcher judges that withdrawing from the study is in the best interest of the subject; the subject has poor compliance.

Subjects voluntarily withdraw from the study due to several reasons: Participants retain the option to terminate their participation in the trial, or if they choose not to discontinue their informed consent, refrain from further medication testing and become unreachable (also known as withdrawal, or dropout). The causes for their withdrawal should be identified and recorded to the fullest extent possible. Researchers are required to attempt to reach out to participants who are unreachable, including a minimum of three telephone attempts. In the event that participants exit the study soon after receiving treatment, relevant follow-up assessments will be carried out.

Criteria for early termination or suspension of the study

1. The frequency and gravity of adverse events observed in this investigation suggest that the continuation of the study would pose significant harm to the participants.
2. During the trial, it was revealed that there were substantial errors in the clinical trial design, complicating the assessment of the efficacy of the drug.
3. The protection of the subjects was inadequate. The sponsor is requesting study termination based on the priority of the rights and safety of the subjects (e.g., financial or managerial considerations).
4. The trial may be halted by the National Medical Products Administration or the Ethics Committee for various reasons.

Pharmacokinetic assessment

Evaluation index

Peak concentrations of QX002N after administration (C_{max}); Area under the concentration-time curve of QX002N from 0 to time t that the concentration of QX002N can be accurately measured (AUC_{last}); Area under the concentration-time curve of QX002N from 0 to infinity (AUC_{inf}); Peak time of QX002N (T_{max}); Terminal phase elimination half-life ($t_{1/2}$); End-phase elimination rate constant (K_{el}); Volume of distribution/apparent volume of distribution (V_d , V_d/F); Clearance/apparent clearance (CL , CL/F); AUC_{0-inf} extrapolation percentage ($AUC_{\%Extrap}$); Average residence time (MRT_{last}); Absolute bioavailability(F)

PK Blood collection time point

Blood samples of approximately 4 mL were gathered from each dosage group at specific time intervals: 0 hours (within 60 minutes before administration) and 1 hour (immediately after the end of administration, IV only), 2 hours (IV only), 4 hours, 8 hours, 12 hours, 24 hours (D2), 48 hours (D3), 72 hours (D4), D5 (96 hours), D6 (120 hours), D8 (168 hours), D11 (240 hours), D15 (336 hours), D22 (504 hours), and D29 (672 hours), D43 (1008 hours), D57 (1344 hours), D71 (1680 hours), D85 (2016 hours), D106 (2520 hours), and D127 (3024 hours).

The SC group obtained 20 blood samples, totaling 80 mL of whole blood, while group IV gathered 22 blood samples, comprising 88 mL of whole blood.

Blood was collected within 5 minutes after the end of administration. Between 2 to 24 hours, the time window for blood collection was within ± 10 minutes, while from day 3 to day 6, it was within ± 60 minutes. From day 8 to day 11, the time window for blood collection was within ± 3

hours. On days 15 to 29, the time window for blood collection was within a day. Finally, from day 43 to day 127, the time window for blood collection was within ± 2 days.

Safety assessment

In clinical studies, it is necessary to document details of any adverse events or serious adverse events experienced by participants. This information should include the name of the event, its clinical features, severity, duration, treatment, outcome, and potential relationship with the investigational drug. Furthermore, evaluation is conducted using vital signs, physical examinations, various laboratory tests (including blood, urine, and coagulation analyses), 12-lead electrocardiograms, injection site reactions, and infusion-related reactions.

Immunogenicity assessment

evaluation index: Fluctuations in the levels of anti-QX002N antibody (ADA), along with the occurrence of antibody-related adverse events when ADA is detected, or abnormal PK values, may necessitate the performance of a neutralizing antibody (NAb) test.

ADA blood collection time point: Each measurement group was subjected to the collection of approximately 4 mL of venous blood samples at specific time points: 0 h (within 60 min prior to administration) as well as D29 (672 h), D57 (1344 h), D85 (2016 h), and D127 (3024 h) following the commencement of administration. For ADA testing, a total of 5 blood collection sites were utilized.

Statistical analysis

General analysis

Descriptive statistics will be completed using SAS 9.4 or above software. Quantitative indicators will be statistically summarized within each group using metrics such as total cases, mean, standard deviation, variation coefficient, median, minimum, and maximum values. The counts within each group will also be outlined, including the number of use cases and their corresponding percentages.

Pharmacokinetic analysis

The Phoenix WinNonlin software version 8.2.0 was utilized for non-compartmental analysis to compute pharmacokinetic parameters based on actual blood sample collection times and concentrations. Descriptive statistical analysis of the PK parameters was conducted by agent group. The absolute bioavailability of subcutaneous QX002N compared to intravenous infusion of QX002N was determined.

The drug time curve for each subject was plotted based on the actual blood collection time and blood drug concentration. Additionally, an average drug time curve was constructed based on the planned blood collection time and blood concentration.

Security analysis

Safety analyses (including demographic data) will include data obtained from all subjects who received one less trial drug. The safety evaluation indicators include the following: vital signs, physical examination, clinical laboratory results (blood routine, blood biochemistry, urine routine, coagulation routine), chest radiograph, 12-lead electrocardiogram, injection site reactions, infusion-related reactions, and AEs/SAEs.

Safety data were analyzed with descriptive statistics. AEs were coded (System Organ Classification [SOC] and Preferred Terminology [PT]) in accordance with the Standard We Academic Phrasebook for Pharmacy Management (MedDRA version 22.0 or above), and the number of occurrences, number of persons with incidence rate of all AEs, ADRs, SAEs, etc. were

summarized and described; SOC and PT summaries were described for the different dosage groups and AEs, and SAEs would be listed separately.

Statistically summarize and list adverse events, serious adverse events, vital signs, physical examinations, laboratory tests (blood routine, blood biochemistry, urine routine and coagulation routine), 12-lead electrocardiogram and other data.

Immunogenicity analysis

Analysis of immunological data is based on immunogenicity analysis of the population. ADAs/NABs were summarized and tabulated descriptively by group. Summary and descriptive tabulation of ADAs/NABs were conducted for each group.