Research Program

(Version number: 02 Version date: 2022-05-03)

Project name: Clinical efficacy and safety of real-world patients with refractory rheumatoid arthritis (D2TRA) treated with Abciap in combination with Janus kinase (JAK) inhibitors

Bidder: Zhejiang Provincial People's Hospital

Department: Rheumatology and Immunology

Principal Investigator: Zhenhua Ying

Investigator's statement and protocol signature page

As the principal person in charge of this research project, I will follow the Ethical Review of Biomedical Research Involving Human Beings (2016) of the Ministry of Health, the Declaration of Helsinki (2013) of the WMA and the International Ethical Guidelines for Human Biomedical Research (2002) of the CIOMS and the ethical principles of the GCP, using the protocol approved by the ethics committee under the guidance of the quality management specifications for drug clinical trials, and conducting the study in accordance with the requirements of this protocol to ensure the scientific validity of the study and to protect the health and rights of the subjects.

Name: _____

Signature: _____

Date: _____

Program Summary

Program Title	Clinical efficacy and safety of real-world patients with refractory rheumatoid arthritis (D2TRA) treated with abciap in combination with Janus kinase (JAK) inhibitors
Version number/version date	02/ 2022-05-03
Sponsors and Participating Units	Zhejiang Provincial People's Hospital
Principal Investigator	
Nature of Research	Clinical Studies
Purpose of the study	To observe the clinical efficacy and safety of Abciap combined with JAK inhibitor in the treatment of D2TRA patients
Sample size	90
Research Subjects	Patients with refractory rheumatoid arthritis
Research Methodology	Real-world observational study. Prospectively, 90 patients with D2TRA who were ineffective to conventional disease-modifying antirheumatic drugs and ineffective to treatment with 2 or more biological/targeted disease-modifying antirheumatic drugs and treated with abciap combined with JAK inhibitors attending the outpatient and inpatient departments of Zhejiang Provincial People's Hospital from March 2022 to March 2024 were included as an observational group. Thirty patients with D2TRA treated with abciap alone in the outpatient and inpatient departments of Zhejiang Provincial People's Hospital from August 2020 to November 2021 were selected as the historical control group. There was no statistically significant difference between the observation group and the control group in terms of gender, age, disease duration, number of pressure pain in 28 joints, number of swelling in 28 joints, and DAS28 score ($P > 0.05$). The drugs were billed according to the maximum number of days of medical insurance (4 weeks), and the changes in laboratory tests, number of pressure pain in 28 joints, number of swelling in 28 joints, and DAS28 score were observed in the group treated with Abacap

	combined with JAK inhibitor, and the before-and-after self comparison was performed at 0, 4, 8, 12, 16, 20, and 24 weeks, along with the changes in joint ultrasound and adverse effects. Also observe the changes in laboratory tests, number of pressure pain in 28 joints, number of swelling in 28 joints, and DAS28 score in the group treated with Abacap alone, and perform a before-and-after self-comparison at 0, 4, 8, 12, 16, 20, and 24 weeks, as well as observe the changes in joint ultrasound and adverse reactions. In addition, we observed the changes in laboratory tests, the number of pressure pain in 28 joints, the number of swelling in 28 joints, and the DAS28 score between the patients in the Abacap combined with JAK inhibitor treatment group and the Abacap treatment group alone at 0, 4, 8, 12, 16, 20, and 24 weeks, and compared them between the two groups for a statistically significant difference at $P < 0.05$. We also observed the changes in joint ultrasound and adverse effects between the two groups. Changes in adverse reactions
Inclusion Criteria	1. Meet the diagnostic criteria for refractory rheumatoid arthritis 2. Patients who have been treated with conventional disease-modifying rheumatic drugs and have been treated with 2 or more biologic/targeted disease-modifying anti-rheumatic drugs and require Abciap in combination with JAK inhibitors
Exclusion Criteria	1. Those who do not meet the above inclusion criteria 2. Patients with tumors, hematological diseases and other autoimmune diseases 3. History of allergy to the drugs selected for this study 4. Patients who cannot adhere to the treatment of Abciap combined with JAK inhibitors, or who have serious adverse reactions and have not completed the observation course specified in the study
Research Progress Plan	2022.03-2024.03
Statistical analysis methods	SPSS software was used for statistical analysis. Normality tests were performed using SPSS software was used for statistical analysis. Normality tests

	were performed using the Kolmogorov-Smirnov test, and measures conforming to a normal distribution were expressed as mean ± standard deviation (x ± s), and comparisons between groups were made using the two independent samples t-test; measures not conforming to a normal distribution were described by median and interquartile spacing, i.e., median (25th percentile, 75th percentile) [M(P25,P75)], and comparisons between groups were made using the Mann-Whitney U anecdotal test The difference between groups was considered statistically significant at $P < 0.05$. The data were analyzed by the chi-square test or Fisher's exact probability method.
Form of publication of research results	Published 1-2 papers

1.Purpose of the study

(1)To observe the effect of Abasip combined with JAK inhibitor on the clinical efficacy of D2TRA patients

(2)To observe the safety of Abciap combined with JAK inhibitor in the treatment of D2TRA patients

2.Background of the study

Rheumatoid arthritis (RA) is a common systemic inflammatory autoimmune disease, and is one of the most common connective tissue diseases with inflammatory joint damage. The disease mainly affects the small joints of the hands, wrists and feet, and is characterized by inflammation of the synovial membrane, with clinical manifestations of symmetrical joint pain and swelling. If left untreated for a long time, it can lead to significant limitation of joint movement or even deformity and disability. In some cases, the inflammation may also cause extra-articular manifestations such as pleural involvement, vasculitis, pericarditis, myocardial infarction, rheumatoid nodules, neurological entrapment syndrome and dry keratoconjunctivitis, etc. The intra- and extra-articular pathologies caused by RA can lead to serious impairment of physical function and quality of life, causing a great burden to the patient, family and society. In addition, RA patients are more prone to serious infections, respiratory diseases, osteoporosis, cardiovascular diseases, and cancer than the general population, and have a relatively higher mortality rate. Therefore, early detection and aggressive treatment are crucial for RA patients.

The treatment of RA is still dominated by drugs, including: non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, biologics, and Chinese herbal medicines. The main effect of these drugs is to control the disease, which can delay but not completely stop the onset and progression of lesions. In the past 30 years, targeted synthetic DMARDs (tsDMARDs, such as pan-JAK and JAK1/2 inhibitors) and biological DMARDs (bDMARDs, such as tumor necrosis factor inhibitors, interleukin-6 inhibitors, B-cell depletion antibodies and co-stimulatory molecule inhibitors) have been widely used in the clinic, making breakthroughs in the treatment of RA, and some RA After treatment, some RA patients are able to significantly improve their disease activity and delay joint deformation.

However, there are some patients whose disease activity is still not effectively controlled. Therefore, according to the 2021 European League Against Rheumatism (EULAR) recommendations, RA is defined as refractory RA (difficult-to-treat rheumatoid arthritis, D2TRA) when the following three criteria are met: (1) failure of csDMARDs after treatment according to the EULAR recommendations (unless there is a contraindication) after failure of ≥2b/tsDMARDs (with a different mechanism of action); (2) presence of at least one of the following: at least moderate disease activity; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid therapy; rapid imaging

progression; RA symptoms leading to decreased quality of life; (3) rheumatologists and/or patients who believe that signs and/or symptoms of treatment is problematic.

Due to the complex etiology and pathogenesis of D2TRA, poor treatment outcomes, insufficient clinical attention and focus, high rates of bone erosion and even joint deformity. In addition, the high incidence of D2TRA is mostly in middle age, which is at the peak of career and belongs to the main group of social work. Once the disability is caused by "failure to treat", it will not only cause the patients' physical function, quality of life and social participation to decrease, but also bring a huge economic burden to the patients' families and society. It is no less harmful than some lethal diseases and other geriatric diseases.

Therefore, it has become an important task in the field of rheumatology and immunology to explore and find new methods and means to treat D2TRA. In the last decade, a variety of novel bDMARDs (e.g., abciap) and tsDMARDs (e.g., JAK inhibitors) have been introduced, all of which have demonstrated fruitful anti-inflammatory and disease activity improvement in the treatment of RA patients. Studies have shown that in patients with RA who are poorly treated with methotrexate or tumor necrosis factor inhibitors, treatment with Abciap (ABT) in combination with methotrexate has been shown to improve joint symptoms, reduce disease activity, slow the deterioration of damaged joint structures and improve physical function.

ABT is a novel immunomodulator that contains the extracellular structural domain of CTLA-4 and the Fc portion of IgG1, a soluble, recombinant, fully humanized fusion protein. The mechanism of action of ABT is to bind to co-stimulatory molecules CD80 and CD86 on antigen presenting cells (APCs), thereby blocking their interaction with CD28 on T cells and achieving immunosuppression. It can be used to treat adult patients with moderate-to-severe RA who have been treated with one or more DMARDs but still have poor therapeutic outcomes, and has demonstrated good clinical efficacy and safety, especially for patients who are anti-CCP antibody positive or HLA-DRB1 co-epitope positive. A prospective, open study showed that both ABT and tolimumab significantly reduced disease activity and improved physical function in RA patients who were not responding to tumor necrosis factor inhibitor therapy. However, ABT not only had fewer adverse effects and better laboratory results, but also had a higher safety profile in both short- and long-term follow-up. A real-world population-based study showed that 1520 patients with RA treated with ABT demonstrated good tolerance to ABT compared with other bDMARDs or csDMARDs, with no increased overall risk of malignancy, infection, or autoimmune disease. However, ABT has the disadvantage of slow onset of efficacy and inadequate pre-treatment response. When it does not respond adequately to treatment, other bDMARDs are usually no longer an option because the risk of comorbidities and drug toxicity has reached low levels. in such cases, the combination of tsDMARDs would be a

practical and reasonable option. A recent prospective, multicenter, observational study in Japan showed that ABT is effective and safe in elderly RA patients with a history of refractory csDMARDs. In both younger and older patients with csDMARDs-refractory RA, ABT was shown to be more effective than adding or switching to new csDMARDs.

JAK inhibitors are a new class of drugs for the targeted treatment of RA and belong to the csDMARDs class. jak kinase is a non-receptor tyrosine protein kinase that mediates cytokine production signaling and is an important intracellular signaling pathway. This transduction pathway plays an important role in the pathogenesis of several inflammatory diseases, such as RA. The mechanism of action of JAK inhibitors is to target the ATP binding sites of JAK1, JAK2 and JAK3, inhibit the phosphorylation of kinases and block the JAK pathway, thus blocking the progression of inflammation at the source, modulating the immune response and improving the patient's condition. A recent study from Japan compared the response to different classes of b/tsDMARDs in D2TRA and vD2TRA patients who were ineffective to various b/tsDMARDs. The results suggest that JAK inhibitors are the preferred treatment option for this type of D2TRA. jAK inhibitors have a rapid onset of action and stable drug efficacy during the action period, which can compensate for the lack of response in the pre-action phase of ABT. In addition, Lindsay Claxton et al. found that the use of JAK inhibitors provides better cost-effectiveness when their efficacy and safety profile is similar to that of other biologic agents. In addition, studies have demonstrated that while there is an increased incidence of mild adverse effects such as diarrhea, elevated total serum cholesterol and lipoproteins, there is no increased risk of serious infections in patients. A recent US study showed that the use of JAK inhibitors in combination with CTLA4-Ig in the presence of inflammatory cytokines maintained the immunomodulatory effects of CTLA4-Ig and promoted long-term survival of murine cardiac allografts. In contrast, activation of inflammatory factors happens to be one of the important pathogenic mechanisms of RA.

Based on the different anti-inflammatory mechanisms and onset of action of ABT and JAK inhibitors, as well as the targeting, safety and economic characteristics of JAK inhibitors, the combination of ABT and JAK therapy may bring new hope to D2TRA patients.

The 2019 European League Against Rheumatism (EULAR) has updated its recommendations for the management of RA in conjunction with the latest research findings in the field. Provides guidance on drug combinations for the treatment of RA. It is considered that when response is still inadequate after 3-6 months of conventional treatment with methotrexate and glucocorticoids, patients should be stratified according to their own risk factors to guide treatment. That is, if poor prognostic factors are present (presence of autoantibodies, high disease activity, early onset of erosion, or failure of both csDMARDs treatments) bDMARDs or JAK inhibitors in combination with csDMARDs should be

added. If this fails, other bDMARDs or tsDMARDs are recommended.Abbasi M et al. comprehensively explored the development of new and recent treatment regimens for RA by combining conventional, newly developed, and still-in-study RA treatment strategies and proposed that the use of biologics or biosimilars alone, or in combination with DMARDs, can further improve RA and is a better treatment options. Therefore, in the face of D2TRA and poor treatment with traditional DMARDs, the use of novel immunosuppressive agents alone or in combination with two immunosuppressive agents is a new therapeutic direction that can be sought.

3.Test basis

(1)Pre-study animal experiments and literature base

Animal experiments： Iglesias M et al. A short course of tofacitinib sustains the immunoregulatory effect of CTLA4-Ig in the presence of inflammatory cytokines and promotes long-term survival of murine cardiac allografts. This study from the United States showed that JAK inhibitors combined with CTLA4-Ig in the presence of inflammatory cytokines maintained the immunomodulatory effects of CTLA4-Ig and promoted long-term survival of murine cardiac allografts. Literature Base： EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update.

Sei Muraoka et al. Abatacept is Efficacious in the Treatment of Older Patients with csDMARD-Refractory Rheumatoid Arthritis: A Prospective, Multicenter, Observational Study.This Japanese prospective, multicenter, observational study demonstrated that abciap is effective and safe in older RA patients with a history of csDMARDs-refractory disease. In both younger and older patients with csDMARDs-refractory RA, abciap was shown to be more effective than adding or switching to new csDMARDs.

Sae Ochi et al. Preferable outcome of Janus kinase inhibitors for a group of difficult-to-treat rheumatoid arthritis patients: from the FIRST Registry.This Japanese study compared the response to different classes of b/tsDMARDs in D2TRA and vD2TRA patients who were not responding to multiple b/tsDMARDs. The results suggest that JAK inhibitors are the preferred treatment option for this type of D2TRA.

(2)Subject selection basis

Patients diagnosed with refractory rheumatoid arthritis who meet the 2021 European League Against Rheumatism (EULAR) diagnostic criteria for refractory rheumatoid arthritis

4.Research Content

(1)Test population: patients with refractory rheumatoid arthritis

(2)Sample size: 90 D2TRA patients

(3)Specific study: 90D2TRA patients who were ineffective to conventional disease-modifying antirheumatic drugs and ineffective to treatment with 2 or more biological/targeted disease-modifying antirheumatic drugs and treated with Abacap combined with JAK inhibitors attending the outpatient and inpatient departments of Zhejiang Provincial People's Hospital from March 2022 to March 2024 were prospectively included as the observation group. Thirty patients with D2TRA treated with abciap alone in the outpatient and inpatient departments of Zhejiang Provincial People's Hospital from August 2020 to November 2021 were selected as the historical control group. There was no statistically significant difference between the observation group and the control group in terms of gender, age, disease duration, number of pressure pain in 28 joints, number of swelling in 28 joints, and DAS28 score ($P > 0.05$). Drugs were billed according to the maximum number of days of medical insurance (4 weeks), and changes in laboratory tests, number of pressure pains in 28 joints, number of swelling in 28 joints, and DAS28 score were observed in the Abciap combined with JAK inhibitor treatment group, and pre- and post-self comparisons were performed at 0, 4, 8, 12, 16, 20, and 24 weeks, along with changes in joint ultrasound and adverse effects. The changes in laboratory tests, number of pressure pains in 28 joints, number of swelling in 28 joints, and DAS28 scores were also retrospectively collected from the group treated with Abacap alone, and before and after self-comparison was performed at 0, 4, 8, 12, 16, 20, and 24 weeks, along with observation of changes in joint ultrasound and adverse effects. In addition, we observed the changes in laboratory tests, the number of pressure pains in 28 joints, the number of swelling in 28 joints, and the DAS28 score at 0, 4, 8, 12, 16, 20, and 24 weeks in the group treated with Abatacept combined with JAK inhibitor and the group treated with Abatacept alone, and compared them between the two groups for a statistically significant difference at $P < 0.05$. We also observed the changes in joint ultrasound and The changes of adverse reactions were also observed between the 2 groups.

5.Research Methodology:

Enrollment criteria (diagnostic criteria, inclusion criteria, exclusion criteria)

(1) Diagnostic criteria

The diagnostic criteria for D2TRA refer to the definition criteria proposed by EULAR 2021:

1. Failure of ≥2b/tsDMARDs (with different mechanisms of action) after failure of csDMARDs therapy (unless contraindicated) according to the European Rheumatology Consortium recommended treatment.

2. Presence of ≥ 1 of the following signs indicative of active/progressive disease.

a. At least moderate disease activity (based on validated composite metrics including

joint counts such as DAS28-ESR > 3.2 or CDAI > 10).

b. Signs (including acute phase reactants and imaging) and/or symptoms (joint related or otherwise) suggestive of active disease.

c. Inability to taper glucocorticoid therapy (prednisone below 7.5 mg/day or equivalent dose).

d. Rapid progression of imaging (with or without signs of active disease).

e. Good control of the disease according to the above criteria, but still have RA symptoms that lead to a reduced quality of life.

3. Rheumatologists and/or patients who perceive signs and/or symptoms as problematic in the treatment.

All three criteria need to be present in D2T RA.

b, Biological; CDAI, clinical disease activity index; cs, conventional synthesis; DAS28-ESR, the disease activity score of 28 joints was evaluated by ESR; DMARD, disease-modifying antirheumatic drug; mg, milligram; RA, rheumatoid arthritis; ts, targeted synthetic.

* Unless restricted by access to treatment due to socioeconomic factors.

† If csDMARD treatment is contraindicated, failure of ≥ 2 b/tsDMARDs with different mechanisms of action is sufficient.

‡ Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥ 5 points at 1 year.

(2) Exclusion Criteria

1. Those who do not meet the above inclusion criteria

2. Patients with tumors, hematological diseases and other autoimmune diseases

3. History of allergy to the drugs selected for this study

4. Patients who cannot adhere to the treatment of Abciap combined with JAK inhibitors, or who have serious adverse reactions and have not completed the observation course specified in the study

6.Test procedure

1. Subject management

Subject recruitment method: Direct recruitment during the clinical care process

2. Informed consent process: Subjects voluntarily joined the study and voluntarily signed the informed consent form.

7.Research Program

No intervention factors were imposed on the study subjects in the study. Prospectively, 90 patients with D2TRA who were ineffective to conventional disease-modifying antirheumatic drugs and ineffective to treatment with 2 or more biological/targeted disease-modifying antirheumatic drugs and treated with Abacap combined with JAK inhibitors attending the outpatient and inpatient departments of Zhejiang Provincial People's Hospital from March 2022 to March 2024 were included as the observation group. Thirty patients with D2TRA treated with abciap alone in the outpatient and inpatient departments of Zhejiang Provincial People's Hospital from August 2020 to November 2021 were selected as the historical control group. There was no statistically significant difference between the observation group and the control group in terms of gender, age, disease duration, number of pressure pain in 28 joints, number of swelling in 28 joints, and DAS28 score ($P > 0.05$). The dosage was 125 mg per dose by subcutaneous injection once a week, and the dosage was 5 mg per dose by oral injection twice a day. The drug was billed according to the maximum number of days of medical insurance (4 weeks), and patients were observed for rheumatoid factor, anti-cyclic citrullinated peptide antibodies, immunoglobulins (IgG, IgA and IgM), C-reactive protein, blood sedimentation, white blood cells, platelets, ghrelin, glutamic aminotransferase, glutamic oxalacetic aminotransferase, globulin, creatinine, glomerular filtration rate, 28 joints at 4, 8, 12, 16, 20 and 24 weeks before and after drug administration number of pressure pain, number of swelling in 28 joints, joint ultrasound, change in DAS28-ESR score and adverse effects. To observe the changes in laboratory test indices, number of pressure pain in 28 joints, number of swelling in 28 joints, and DAS28 scores in the Abciap combined with JAK inhibitor treatment group, before and after self-comparison at 0, 4, 8, 12, 16, 20, and 24 weeks, as well as the changes in joint ultrasound and adverse effects. Also retrospectively collected the changes in laboratory test indices, number of pressure pain in 28 joints, number of swelling in 28 joints, and DAS28 score in the group treated with Abacap alone, and performed a before-and-after self-comparison at 0, 4, 8, 12, 16, 20, and 24 weeks, while observing the changes in joint ultrasound and adverse effects. In addition, we observed the changes in laboratory indices, the number of pressure pain in 28 joints, the number of swelling in 28 joints, and the DAS28 score between the Abciap and JAK inhibitor treatment groups at 0, 4, 8, 12, 16, 20, and 24 weeks, and compared them between the two groups. The changes in joint ultrasound and adverse effects between the two groups were also observed, so as to observe the clinical efficacy and safety of the Abciap combined with JAK inhibitor treatment group. $DAS28 \leq 2.6$ was defined as clinical remission, $2.6 < DAS28 \leq 3.2$ as low activity, $3.2 < DAS28 \leq 5.1$ as moderate activity, and $DAS28 > 5.1$ as high activity.

8.Start and end of the experiment

2022.03-2024.03

9.Data Security and Monitoring Program

(This paragraph cannot be deleted, if not, fill in none. According to the requirements of the Ministry of Health's Measures for Ethical Review of Biomedical Research Involving Human Beings (2016), all research projects are required to have a data security and monitoring plan, and this item is one of the criteria for the ethics committee to review the project, please describe it specifically according to the requirements.)

(1) *Overview of data management methods*

1.Data are traceable. All clinical trial data correspond to specific subjects and investigators, and all modifications to the data are recorded in detail to create a series of traceable verification traces.

2.Correctness of data. The correctness of data mainly includes the authenticity and accuracy of data, all clinical trial data reflect the actual situation of the study truthfully without any falsification, fiction and tampering; the accuracy is reflected in the verifiable data sources, i.e. CRF, study records and entered data should be consistent with the data obtained from the actual study.

3.Data completeness. Study data were collected completely for each subject, and missing data due to special reasons were stated as to why they were missing.

4.Logical reasonableness of the data. To determine whether the data are logically unreasonable from a clinical perspective.

5.Timeliness of data. The data are observed and completed in a timely manner at the specified time points in the clinical trial.

(2) Adverse events and serious adverse events are reported and collected.

Reporting principles: 1. Report only adverse events related to the study drug 2. Complete the Spontaneous Adverse Event Report Form for all related adverse events (serious and non-serious)

The following information should also be included to determine if the event is related, possibly related, or potentially related to the drug. Determination of event-drug relevance includes: 1. reasonable temporal sequence 2. dose-response relationship 3. pharmacology 4. discontinuation of dosing and/or positive re-dosing.

Classification of the severity of drug-related adverse events：

Mild	The symptoms do not alter the patient's normal function.
Moderate	The symptoms result in some degree of functional impairment, but are not damaging, uncomfortable, or embarrassing.
Severe	The symptoms are definitely detrimental to health, with significant

	functional impairment or incapacity.

3) Medical safety measures

1.Collect information, focus on prevention. Supervise the department to report the risk information of clinical medical research in a timely manner, so that the information monitoring is in place and the risk prevention is effective.

2.Early warning, timely disposal. The department strengthens the monitoring of risks, regularly monitors and inspects, and once problems are found, reports them to the department head in a timely manner and takes decisive measures to control and resolve the risks in a timely manner, prevent the expansion and spread of risks, and minimize them.

3.We regularly assess risks and propose corrective measures to prevent them.

4.Before clinical research begins, the investigator must provide the subject with information about the treatment and the subject's rights and obligations, so that the subject fully understands and agrees to it, and signs an "informed consent" before the clinical research experiment can begin.

If one of the following situations occurs, the emergency handling procedures should be started immediately to stop the scientific clinical medical research and report to the Science and Education Section.

1.The research clinical medical research in the technical staff or key equipment, facilities and other auxiliary conditions change, can not properly carry out clinical research or may bring uncertain consequences.

2.The occurrence of serious adverse consequences directly related to the research clinical medical study.

3.The ethical flaws in this research-based clinical medical study.

4.The medical quality and medical safety risks associated with this research-based clinical medical study.

5.The clinical application of this research-based clinical medical study is inexact.

4) Communication with ethics committee and higher pharmacovigilance department

1.The research protocol needs to be developed and submitted to the Medical Ethics Committee for approval prior to the start of the project.

2.The project research should be filed with the higher drug regulatory authorities in a timely manner, and actively accept the guidance and supervision of the higher drug regulatory authorities.

5） Internal analysis plan for data

1.Data Collection

Information about patients who met the enrollment criteria and data from laboratory-related tests

were collected.

①Case collection form: includes basic information of enrolled patients, related diseases, disease duration, treatment, and test data of related indicators for individual data analysis.

②Summary table: includes the patient's disease and related index examination data for overall data analysis.

2.Assessing the overall data situation

①Evaluate the integrity of each data source: timely recording of patient-related data to ensure data integrity.

②Evaluate the accuracy and consistency of aggregated data: randomly check whether the extracted data are consistent with those in the database to ensure data accuracy.

3.Data cleaning and collation

①Check for errors and outliers in the data that clearly defy common sense, and when found, first check that the same patient metadata are the same, then check how this data was collected, and finally how to assess whether it is an outlier from a technical point of view, by using relevant statistical indicators and methods such as setting upper and lower limits to deal with outliers.

②For special numbers, first mark "missing value", there is a perfect data dictionary to query the actual situation of this field, if not need to promptly communicate to confirm such issues

4.Data Collation

①Uniform formatting and naming rules for data

②Recoding of certain information to meet subsequent analysis needs

5.Data Visualization

Histograms, line graphs, scatter plots or heat maps are used to visualize the data of patient-related indicators to show the data results and trends more clearly, so that the study results can be presented more clearly.

6.Data Analysis

Complete the data and perform statistical analysis on those that meet the criteria

1） Frequency of data security and monitoring reports submitted to the ethics committe

The research in this project is a low-risk study, so an annual review frequency is used. Also, the principal investigator holds regular study meetings and notifies the ethics committee if there are changes in the risk/benefit ratio of the study.

10.Respect for ethical principles and related regulations

The study was conducted in strict compliance with international and domestic standards and norms,

including the Declaration of Helsinki ethical guidelines for human medical research and the relevant Chinese clinical research study norms and regulations. In the course of the study, if there is a need to revise this protocol, the revised protocol must be submitted to the Ethics Committee again for approval before implementation.

The Informed Consent Form for this study has been approved by the Medical Ethics Committee. If the Informed Consent Form is amended in writing, it will be sent to the Ethics Committee for approval to obtain the subject's consent again. Before the start of the study, the investigator provides patients with detailed information about the study, including the nature of the study, the purpose of the study, the possible benefits and risks, and the rights and obligations of the patients. The patient is fully informed and agrees, and signs the Informed Consent Form before the study can begin.

11.Statistical analysis plan

SPSS software was used for statistical analysis. Normality tests were performed using the Kolmogorov-Smirnov test, and measures conforming to a normal distribution were expressed as mean ± standard deviation (x ± s), and comparisons between groups were made using the two independent samples t-test; measures not conforming to a normal distribution were described by median and interquartile spacing, i.e., median (25th percentile, 75th percentile) [M(P25,P75)], and comparisons between groups were made using the Mann-Whitney U anecdotal test Comparisons between groups were made using the Mann-Whitney U anecdotal sum test; count data were expressed as percentages, and comparisons between groups were analyzed using the chi-square test or Fisher's exact probability method, with differences considered statistically significant at $P < 0.05$.

12、Form of publication of research results

Published 1-2 papers

13.Data Logging Form

Observed indicators		Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Rheumatoid factor	IU/ml							
Anti-cyclic citrulli	U/ml							

nated peptide antibody								
Immunoglobulin G	g/L							
Immunoglobulin A	g/L							
Immunoglobulin M	g/L							
C-reactive protein	mg/L							
Blood sedimentation	mm/h							
Leukocytes	$x10^9$/L							
Blood platelets	$x10^9$/L							
Glutathione aminotransferase	U/L							
Glutathione transa	U/L							

minase								
Globulin	g/L							
Creatinine	umol/L							
Glomerular filtration rate	ml/min							
Glomerular filtration rate	pcs							
Swollen number of 28 joints	pcs							
DAS28-ESR score	score							
Ultrasound of joints								

14.Adverse reaction record form

No adverse events have occurred	□yes □no
Name of undesirable events	
Start date of occurrence	_____Year_____month_____day
Dosing time and dosage	_____ year _____ month _____ day _____mg
Severity*	□ Mild □ Moderate □ Severe
Whether to take	□yes ☐no

measures	
Relationship to study drugs	□Definitely related □Likely related ☐ Possibly related ☐ Possibly unrelated ☐Definitely not related
Outcome of adverse events that occurred	□Still exists ☐Eased □No idea Relief Date_____ year _____ month _____ day
Whether the patient withdrew from the trial because of the adverse event	□yes □no

Severity*: mild (no treatment, no discontinuation), moderate (discontinuation, no treatment), severe (discontinuation, control treatment)