Clinical Protocol

Efficacy and Safety of Ivarmacitinib for Polymyalgia Rheumatica (ESI-PMR): A 52-Week Open-Label, Randomized, Controlled Clinical Trial

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Sub-centers: the Fourth Affiliated Hospital, Zhejiang University School of Medicine, Wenzhou People's Hospital, Huzhou First People's Hospital, Anji People's Hospital, and Haining Kanghua Hospital

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Investigator statement and signature page

This study is a prospective clinical study, and the methodology and drugs used in the study have been widely used clinically. This study will establish a strict adverse event monitoring system to carefully record all adverse events that occur and deal with them in a timely and effective manner. In case of any serious adverse event or important adverse event, no matter whether it is related to the research intervention or not, and no matter whether the intervention operation has been implemented or not, the research sponsor must be notified in time, and the researcher should decide whether to stop the research in a timely manner according to the situation. The researchers guarantee that the personal data of the subjects will be kept strictly confidential: all subject information and images will be identified by numbers rather than names; identifiable information will not be disclosed to members outside the research team, unless the subjects are obtained All research members and research sponsors are required to abide by the principle of confidentiality; all research files will be kept in locked filing cabinets, which are only available to researchers; during the implementation of the research and after completion, government management departments are allowed Or the members of the ethics committee will conduct spot checks and supervision on the personal data of the subjects according to the regulations; when the results of this research are published, no personal data will be disclosed.

Researcher's signature

I have read and agreed to the plan proposed in this document, and I agree with the relevant content of the plan. During the experiment, I will strictly abide by the laws and regulations of the People's Republic of China and relevant rules and regulations, perform the duties of the researcher and abide by the confidentiality regulations.

Institution ： _____

Name： _____

Position： _____

Signature： _____

Date： _____

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Abstract

Title	Efficacy and Safety of Ivarmacitinib for Polymyalgia Rheumatica (ESI-PMR): A 52-Week Open-Label, Randomized, Controlled Clinical Trial
Disease	Polymyalgia Rheumatica (PMR)
Objective	Assess the efficacy and safety of Ivarmacitinib in patients with PMR
Institution	the First Affiliated Hospital, Zhejiang University School of Medicine, the Fourth Affiliated Hospital, Zhejiang University School of Medicine, Wenzhou People's Hospital, Huzhou First People's Hospital, Anji People's Hospital, and Haining Kanghua Hospital
Participants	Patients who met the inclusion criteria and were not in exclusion criteria
Sample	We will recruit 72 cases to the Ivarmacitinib treatment group and 72 cases to the control treatment group
Drugs	Ivarmacitinib，4mg, tablet
Dosage regimen	**Treatment group:** Prednisone (or equivalent dose of methylprednisolone) + Ivarmacitinib (Withdrawal of prednisone within 8 weeks: 15mg daily for 2 weeks, 10mg daily for 4 weeks, 5mg daily for 2 weeks, then discontinue) (Take Ivarmacitinib 4mg daily for 24 weeks, then 2mg daily for 28 weeks. If relapses occured during the tapering process, celecoxib may be added. If reducing Ivarmacitinib dosage is difficult, Methotrexate (MTX) 10mg qw can be added after 24 weeks.) **Positive control group:** Prednisone (or equivalent dose of methylprednisolone) (Prednisone 15mg daily was set as the initial treatment of PMR. When improvement was achieved, the dose of Prednisone was reduced to 10mg daily within 4-8 weeks; When remission was achieved, then taper Prednisone gradually by 2.5mg every 10 weeks. Once relapse occurred, the dose increased to the pre-relapse dose. If reducing pred dosage is difficult, MTX 10mg qw can be added after 24 weeks. celecoxib may be added in some cases)
Inclusion criteria	1. patients who fulfilled the 2012ACR/EULAR criteria for PMR； 2. Patients with high activity rheumatic polymyalgia: disease activity score PMR-AS > 10, 3. Adults age 50-88, Weight 45-85Kg, 4. ESR>40mm/h or CRP >50mg/L（5mg/dl）, 5. Informed consent.
exclusion criteria	1. Patients with known allergies to Ivarmacitinib, prednisone or

	methylprednisolone, 2. Patients with identified giant cell arteritis, systemic lupus erythematosus, rheumatoid arthritis, calcium pyrophosphate deposition (CPPD) arthropathy, and other rheumatic diseases, 3. Patients with severe osteoarthritis, 4. Subjects with any severe acute, chronic or recurrent infection (e.g. pneumonia or pyelonephritis, recurrent pneumonia, chronic bronchiectasis, tuberculosis, etc.), 5. Hepatitis B virus carriers or individuals with chronic active hepatitis B or C, other chronic liver diseases, HIV infection, 6. Patients with abnormal liver function (ALT/AST 2 times higher); Moderate to severe renal impairment (glomerular filtration rate <60); hyperlipidemia not improved by lipid-lowering drugs, 7. Pregnant or lactating women, 8. Patients with a history of malignancy who do not meet the following condition (patients with malignant tumors who have been successfully treated for more than 5 years before screening without any evidence of recurrence), 9. Patients with previous visual field disorder or single eye dysfunction, cataract patients, 10. Patients with decompensated cardiac insufficiency or severe hypertension or diabetes mellitus, i.e. systolic blood pressure higher than 160mmhg or diastolic blood pressure higher than 100mmhg, 11. For patients with abnormal blood routine, lymphocytes <500/mm^3 or ANC <1000/mm^3 or HGB < 90g/L, 12. Patients with active bleeding and peptic ulcer, 13. Have used biological agents or added azathioprine, FK506 within 1 month before enrollment, 14. Those who have participated in other drug clinical trials within 4 weeks
Randomization	Randomization was performed using a central randomization system.
Follow-up	Screening、Weeks 0、2、4、8、12、16、24、32、40、48、52
Outcomes	Primary outcomes: Proportion of patients in remission at weeks 24 Secondary outcomes: Proportion of patients in remission at weeks 52, PMR-AS score, CRP, ESR at weeks 24; Relapse rate, Relapse times, Cumulative dose of prednisone, and Cumulative dose of MTX within 52 weeks
Safety	1. Observe the occurrence of adverse events and adverse reactions such as infection, herpes zoster, rash;

	2. Laboratory abnormalities found in blood and urine routine tests, liver, and kidney function, etc.; 3. Abnormal findings in general physical examination (such as heart rate and blood pressure); 4. lumbar fracture, femoral head necrosis; 5. DVT, new cancer, Glaucoma，etc.
Interim analysis	Assess and monitor the progress of the clinical trial, recruitment and screening of participants, data collection and analysis at 16 weeks, etc., if more than half participants enrolled, to ensure the progress and quality of the trial.
Analysis	For the primary efficacy analysis: PPS and FAS analysis set; For the second efficacy analysis: PPS and FAS analysis set; For the safety analysis: SS analysis set.

Abbreviation

Abbreviation	Full name
ACPA	Anti-CCP antibody
AE	Adverse event
ALB	Albumin
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
APTT	Partially activated prothrombin time
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CPPD	Calcium pyrophosphate deposition
CRE	Creatinine
CRF	Case report form
CRP	C reactive protein
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
FAS	Full Analysis Set
GCP	Good Clinical Practice
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HLA-B27	Human leukocyte antigen B27
IL	Interleukin
ITT	Intention-to-Treat
JAK	Janus kinase
MPO	Anti-myeloperoxidase antibody
MTX	Methotrexate
PMR-AS	Polymyalgia rheumatica disease activity score
PPS	Per-protocol dataset
PR3	Anti-Serine Proteinase 3 antibody
RF	Rheumatoid factor
SAE	Serious adverse event

SS	Security set
STAT	Signal transducer and activator of transcription
ULN	Upper limit of normal
WBC	White blood cell count

Flowchart

Weeks of follow-up	Weks -4 ~0	Follow-up1 Wek 0	Follow-up2 Wek2±3d	Follow-up3 Wek4±5d	Follow-up4 Wek8±5d	Follow-up5 Wek12±5d	Follow-up6 Wek16±5d	Follow-up7 Wek24±5d	Follow-up8 Wek32±5d	Follow-up9 Wek40±5d	Follow-up10Wek48±5d	Follow-up 11 Wek52±5d
Sign the informed consent	√											
Inclusion/Exclusion	√											
Demographics	√											
Past medical history	√											
Vital signs	√	√	√	√	√	√	√	√	√	√	√	√
Weight and height	√											
Physical examination	√	√	√	√	√	√	√	√	√	√	√	√
PMR-AS score	√		√	√	√	√	√	√	√	√	√	√
Patient pain VAS Score	√		√	√	√	√	√	√	√	√	√	√
Physician global assessment	√		√	√	√	√	√	√	√	√	√	√
Morning stiffness (min)	√		√	√	√	√	√	√	√	√	√	√
Difficulty in raising upper arm	√		√	√	√	√	√	√	√	√	√	√
Difficulty in squatting and standing up	√		√	√	√	√	√	√	√	√	√	√
ESR	√		√	√	√	√	√	√	√	√	√	√
CRP	√		√	√	√	√	√	√	√	√	√	√

Blood routine	√		√	√	√	√	√	√	√	√	√	√
Urine routine	√		√	√	√	√	√	√	√	√	√	√
Liver function	√		√	√	√	√	√	√	√	√	√	√
Renal function	√		√	√	√	√	√	√	√	√	√	√
Blood glucose	√		√	√	√	√	√	√	√	√	√	√
Coagulation indicators	√											
Immunological test [1]	√											
Hepatitis B test, HBV-DNA	√											
T-spot	√											
Chest X-ray or CT	√											
PET-CT	optional											optional
Shoulder and hip MRI	optional											optional
Bone mineral density	√											√
Electrocardiogram	√											
Randomization		√										
Concomitant medication	√	√	√	√	√	√	√	√	√	√	√	√
Adverse event	√	√	√	√	√	√	√	√	√	√	√	√

Note: 1. Immunological test: rheumatoid factor (RF), anti-CCP antibody, Human leukocyte antigen B27 (HLA-B27), anti-nuclear antibody (ANA), anti-ENA antibody, immunoglobulin and complement levels, anti-myeloperoxidase antibody (MPO), anti-proteinase 3 antibody (PR3).

Backgroud

Rheumatic polymyalgia (PMR) is more common in elderly patients over 50 years old, manifested as pain in the neck, shoulder joints, scapular muscles, and pelvic muscles，often accompanied by systemic symptoms such as fever, fatigue, weight loss. Serum inflammatory markers (such as erythrocyte sedimentation rate - ESR and C-reactive protein - CRP) were increased [1]. The etiology of PMR is not yet fully understood, but current research has found various endogenous and exogenous factors such as genetics, infection, injury, immunity, and inflammation related to the occurrence and development of PMR. The inflammatory factor interleukin (IL)-6 is associated with the onset of PMR, and IL-6 inhibitors can effectively improve the condition of PMR[2]. Among them, IL-6 is considered one of the most important inflammatory factors in PMR, which can continuously amplify the inflammatory response and play an important role in the pathogenesis of PMR through activating the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. In recent years, more and more studies have confirmed that the continuous activation of the IL-6/JAK/STAT signaling pathway is an important pathogenesis mechanism of PMR. Our previous transcriptome study also found that the JAK/STAT-related inflammatory pathways were significantly enriched in peripheral blood immune cells of PMR patients [3], suggesting that the JAK signaling pathway may be an important therapeutic target for PMR, providing a theoretical basis for the application of JAK inhibitors in PMR.

Currently, glucocorticoids are the main treatment for PMR, providing rapid pain relief, reducing inflammatory markers, and improving quality of life. However, the overall duration of steroid treatment is at least one year, and tapering off steroids can lead to relapses. Approximately 40% to 60% of patients experience disease recurrence during the dose reduction process, and about 30% of patients require long-term maintenance of glucocorticoid therapy. PMR patients themselves have a high incidence of osteoporosis, diabetes, cardiovascular disease, and other chronic conditions, and steroid use can lead to various side effects such as osteoporosis, peptic ulcers, steroid-induced diabetes, glaucoma, secondary infections, and metabolic disorders. Some PMR

patients require high doses of steroids at the start of treatment and may also have a poor response to other medications. Therefore, finding better treatment options is an urgent clinical issue to address. Currently, MTX was recommended as a steroid-sparing treatment option for some patients, but the overall efficacy is limited. In recent years, the IL-6 receptor antagonist tocilizumab has demonstrated promising efficacy in treating patients with relapsed or refractory PMR. However, its route of administration, risk of adverse events, and high financial burden have constrained its widespread application among PMR patients in China. Consequently, there is an urgent need to explore safer, more effective, and more accessible therapeutic strategies.

Ivarmacitinib is a highly selective JAK1 inhibitor approved for the treatment of various immune-mediated disorders, including rheumatoid arthritis [4], ankylosing spondylitis [5, 6], atopic dermatitis, and alopecia areata. Multiple randomized controlled trials (RCTs) have demonstrated that ivarmacitinib significantly reduces disease activity in patients with inflammatory diseases while maintaining a favorable overall safety profile. Its primary adverse events—such as upper respiratory tract infections, herpes zoster, and mild laboratory abnormalities—align with the known safety class effects of JAK inhibitors. Given that PMR shares common inflammatory mechanisms with rheumatoid arthritis, particularly the dysregulation of the IL-6/JAK/STAT signaling pathway, ivarmacitinib provides a strong mechanistic rationale and represents a promising novel therapeutic option for PMR.

Our previous 24-week randomized open-label study (PLOS Medicine article) confirmed that tofacitinib (5 mg bid) monotherapy effectively improved symptoms in newly diagnosed PMR patients (not using steroids) with good safety, but there is currently a lack of long-term efficacy and safety data. Another JAK inhibitor, baricitinib, used in combination with low-dose steroids, was found to reduce disease activity in five refractory PMR patients and significantly reduce the use of steroids with good safety [7]. These studies suggest that JAK inhibitors have a promising application prospect in the treatment of PMR. Therefore, it is necessary to conduct well-designed clinical studies to further evaluate the efficacy and safety of Ivarmacitinib in treating PMR.

It should be noted that Ivarmacitinib has not yet been approved by the National

Medical Products Administration for the treatment of PMR. Therefore, this study is an investigator-initiated off-label clinical study. This study will be carried out with full informed consent, strictly following the Good Clinical Practice (GCP) regulations and the research protocol approved by the ethics committee, setting up a complete screening, follow-up and safety monitoring system to maximize the protection of the rights and interests of the subjects and the quality of the research.

Given the rapid onset of action of glucocorticoids and the capability of JAK inhibitors to sustain remission while minimizing steroid exposure, this study proposes a novel regimen: short-term glucocorticoid combined with ivarmacitinib for remission induction, followed by prompt glucocorticoid withdrawal and ivarmacitinib maintenance. Initiating this strategy in the early stage of disease aims to achieve rapid anti-inflammatory control while accelerating steroid discontinuation, thereby reducing cumulative glucocorticoid exposure and associated toxicity. We will evaluate the 52-week efficacy and safety of this investigational strategy. Designed as a clinical trial, the study employs current guideline-recommended standard-of-care glucocorticoid therapy as the active control. This ensures that control arm subjects receive validated standard treatment, adhering fully to ethical standards.

Objectives

2.1 Primary objective

To evaluate the efficacy of the combination of Ivarmacitinib and short-term glucocorticoid induction for remission and rapid discontinuation of glucocorticoids in the treatment of PMR, and to compare the differences in the proportion of patients in remission at weeks 24 between the experimental group and control group.

2.2 Secondary objectives

(1) To evaluate the Proportion of patients in remission at weeks 52 for both groups;

(2) To compare the PMR-AS scores, ESR and CRP levels at weeks24 between the two groups;

(3) To evaluate the Relapse rate and Relapse times within 52 weeks for both groups;

(4) To evaluate the cumulative doses of prednisone and MTX used within 52 weeks for both groups;

(5) To evaluate the effect of the Ivarmacitinib combination regimen in reducing glucocorticoid exposure;

(6) To evaluate the safety of Ivarmacitinib in treating PMR patients over 52 weeks, including the occurrence of infections, herpes zoster, abnormal laboratory indicators, thrombotic events and other adverse events.

,Study design

3.1 Design

This study was a randomized, multi-center, prospective study followed the GCP principles. The whole test will be completed by the multi-research centers according to the protocol.

3.2 Randomization

Randomization was conducted via an Interactive Web Response System / Central Randomization System. Following eligibility confirmation and written informed consent, participants were randomly allocated in a 1:1 ratio. The random allocation sequence was generated by an independent statistician using a computer-generated random number table. Center-stratified block randomization was applied to ensure balanced group distribution across study sites. Investigators were strictly blinded to sequence generation and could not influence allocation. In the event of central randomization system failure, sealed, opaque, sequentially numbered emergency backup envelopes were activated.

3.3 Sample and allocation

3.3.1Sample

We will recruit 72 cases to the Ivarmacitinib+prednison treatment group and 72 cases to the control group.

3.3.2 Allocation

Patients who met the inclusion criteria and were not in exclusion criteria

,Subjects

4.1 Inclusion criteria

（1） PMR patients who fulfilled 2012ACR/EULAR criteria (Table 1) for PMR；

（2） Patients with high activity rheumatic polymyalgia: disease activity score PMR-AS (Table 2) > 10,

（3） Adults age 50-88, Weight 45-85Kg,

（4） ESR>40mm/h or CRP >50mg/L (5mg/dl),

（5） Informed consent.

4.2 Exclusion criteria

（1） Patients with known allergies to Ivarmacitinib, prednisone or methylprednisolone;

（2） Patients with giant cell arteritis, systemic lupus erythematosus, rheumatoid arthritis, CPPD arthropathy, and other rheumatic diseases;

（3） Patients with severe osteoarthritis;

（4） Subjects with any severe acute, chronic or recurrent infection (e.g. pneumonia or pyelonephritis, recurrent pneumonia, chronic bronchiectasis, tuberculosis, etc.);

（5） Individuals carrying hepatitis B virus or with chronic active hepatitis B, hepatitis C, other chronic liver diseases, or HIV infection.

（6） Patients with abnormal liver function (ALT/AST 2 times higher); Individuals with moderate to severe renal impairment (glomerular filtration rate <60); Hyperlipidemia that cannot be corrected with lipid-lowering medications.

（7） Pregnant or lactating women;

（8） Patients with a history of malignancy who do not meet the following condition (patients with malignant tumors who have been successfully treated for more than 5 years before screening without any evidence of recurrence);

（9） Patients with previous visual field disorder or single eye dysfunction, cataract patients;

（10） Patients with decompensated cardiac insufficiency or severe hypertension or diabetes mellitus, i.e. systolic blood pressure higher than 160mmhg or diastolic blood pressure higher than 100mmhg;

（11） For patients with abnormal blood routine, WBC < 2 x 10^9 / L, HGB < 60g / L, or PLT < 50 x 10^9 / L, it is up to the doctor to determine whether the drug can be used;

（12） Patients with active bleeding and peptic ulcer;

（13） Have used biological agents 1 months before enrollment; or Added azathioprine, FK506 within 1 month before enrollment;

（14） Those who have participated in other drug clinical trials within 4 weeks.

4.3 Exit (loss)

Enrolled cases who did not complete the clinical protocol due to the following reasons should be considered dropped out:

(1) Some comorbidities, complications or special physiological changes have occurred

in the subjects in the clinical trial, such as tumors, who are not suitable for continuing research;

(2) Poor compliance of subjects, affecting safety and efficacy evaluators;

(3) Subjects who have adverse events or serious adverse events, such as menopause for more than 3 months, hospitalization, severe infection, or other serious adverse events, are not suitable for continuing the trial;

(4) Patients who are given prohibited drugs or treatments specified in the protocol after randomization;

(5) The subject is unwilling to continue the clinical trial and voluntarily withdraws;

(6) lost to follow-up;

(7) Other situations where the researcher judges that it is necessary to withdraw from the trial.

Processing principles:

For cases dropped out of the trial or lost to follow-up, researchers should actively take measures to complete the last test as much as possible for the analysis of its efficacy and safety.

For all dropped cases, the test conclusion form, and the reasons for the dropped cases should be filled in the case report form. Generally, These are, occurrence of adverse events (including adverse drug reactions and allergic reactions), lack of curative effect (disease or complications), violation of the trial protocol (including poor compliance), loss of follow-up (including subject voluntary withdrawal) test), and others.

4.4 Withdrawal

(1) After the case is enrolled, it is found that those who do not meet the inclusion criteria or meet the exclusion criteria;

(2) Those who have not taken medication after the case is enrolled;

(3) After the case is enrolled, it is automatically dropped out and lost to follow-up, and there is no post-treatment visit record.

The reasons for the excluded cases should be explained, and the case information should be kept complete for future reference. Statistical analysis of efficacy will not be performed, but those who have received at least one treatment and have safety records can participate in safety analysis as appropriate.

4.5 Termination

When clinical trial has not ended according to the plan, and the trial is stopped

halfway. The purpose of the trial suspension is mainly to protect the rights and interests of the subjects, ensure the quality of the trial, and avoid unnecessary economic losses.

During the trial, if there are major mistakes in the established plan or major deviations in the operation process, making it difficult to evaluate the efficacy of drugs.

Treatment

5.1 Study drugs

Ivarmacitinib，4mg, 28 tablets per box；Buy One, Get One Free

5.2 Oral administration

Treatment group: Prednisone (or equivalent dose of methylprednisolone) + Ivarmacitinib

(Withdrawal of prednisone within 8 weeks: 15mg daily for 2 weeks, 10mg daily for 4 weeks, 5mg daily for 2 weeks, then discontinue)

(Take Ivarmacitinib 4mg daily for 24 weeks, then 2mg daily for 28 weeks. If relapses occured during the tapering process, celecoxib may be added. If reducing Ivarmacitinib dosage is difficult, MTX 10mg qw can be added after 24 weeks.)

Positive control group: Prednisone (or equivalent dose of methylprednisolone)

(Prednisone 15mg daily was set as the initial treatment of PMR. When improvement was achieved, the dose of Prednisone was reduced to 10mg daily within 4-8 weeks; When remission was achieved, then taper Prednisone gradually by 2.5mg every 10 weeks. Once relapse occurred, the dose increased to the pre-relapse dose. If reducing pred dosage is difficult, MTX 10mg qw can be added after 24 weeks. celecoxib may be added in some cases)

Screening、Weks 0、2、4、8、12、16、24、32、40、48、52, totally 12 times

Primary outcomes: Proportion of patients in remission at weeks 24

Secondary outcomes: Proportion of patients in remission at weeks 52, PMR-AS score, CRP, ESR at weeks 24; Relapse rate, Relapse times, Cumulative dose of prednisone, Cumulative dose of MTX druing 52 weeks

(Allow celecoxib 200mg once daily or other similar drugs. The cumulative dosage

should be recorded. Concomitant administration of gastric protectants, calcium and vitamin D supplements, anti-osteoporosis agents, as well as antihypertensive, hypoglycemic, and lipid-lowering medications was permitted during the study. Conversely, co-administration of other JAK inhibitors, IL-6 inhibitors, TNF inhibitors, other biological agents, and novel immunosuppressants (unless explicitly specified in the study protocol) was strictly prohibited.

5.3 Randomization

Upon enrollment, after receipt of written informed consent and prior to any study-related procedures, each subject will be assigned a unique sequential random subject number for identification during the study. We use Central Randomization System to generate the randomize numbers for identification during the study period. Participants will be randomly assigned to groups and receive either the medication or initiate the appropriate treatment regimen.

5.4 Treatment and follow up

Course of treatment: to observe the curative effect and safety of 24 weeks and 52 weeks.

Study procedures

6.1 Screening phase: (Weks -4 to Week 0) Screening the participants

(1) Sign the informed consent;

(2) Check the inclusion and exclusion criteria;

(3) Obtain past medical history and demographic data;

(4) Vital signs and physical examination;

(5) Disease assessment: PMR-AS score, pain VAS score, Patient self-assessment, Physician global assessment, morning stiffness time (min), difficulty in shoulder joint lifting (0, 1, 2, 3), difficulty in squatting and standing (0, 1, 2, 3, 4)

(6) Laboratory examination:

Blood routine: red blood cell count, hemoglobin, white blood cell count, platelet count, neutrophil count, lymphocyte count

Urine routine: urine protein, urine red blood cells, urine white blood cells

Liver function: ALT, AST, albumin (ALB)

Renal function: blood urea nitrogen (BUN), creatinine (CRE)

Blood lipids: Total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides

Blood glucose

Coagulation indicators: prothrombin time, activated partial thromboplastin time, fibrinogen

CRP, ESR

Immunological test: rheumatoid factor (RF), anti-CCP antibody (ACPA), Human leukocyte antigen B27 (HLA-B27), anti-nuclear antibody (ANA), anti-ENA antibody, immunoglobulin and complement levels, anti-myeloperoxidase antibody (MPO), anti-proteinase 3 antibody (PR3).

(7) Electrocardiogram;

(8) Chest X-ray or CT

(9) Hepatitis B antigen, antibody, HBV-DNA; T-spot;

(10) PET/CT, MRI scan of shoulder and hip (optional);

(11) Bone mineral density;

(12) Record the concomitant medication and adverse events;

6.2 Follow-up 1 Weks 0

(1) Vital signs and physical examination;

(2) Randomization;

(3) Start drug treatment;

(4) Record concomitant medication and adverse events;

(5) Make an appointment for the next visit;

6.3 Follow-up 2 (Weks2±3 days), 3 (Weks4±5 days), 4 (Weks 8±5 days), 5 (Weks 12±5 days), 6 (Weks16±5 days), 7 (Weks 24±5 days), 8 (Weks 32±5 days), 9 (Weks40±5 days), 10 (Weks 48±5 days)

(1) Vital signs and physical examination;

(2) Disease assessment: PMR-AS score, pain VAS score, Patient self-assessment, Physician global assessment, morning stiffness time (min), difficulty in shoulder joint lifting (0, 1, 2, 3), difficulty in squatting and standing (0, 1, 2, 3, 4)

(3) Laboratory examination:

Blood routine: red blood cell count, hemoglobin, white blood cell count, platelet count, neutrophil count, lymphocyte count

Urine routine: urine protein, urine red blood cells, urine white blood cells

Liver function: ALT, AST, ALB

Renal function: BUN, CRE

Blood lipids: Total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides.

Blood glucose

CRP, ESR

(4) Drug treatment;

(5) Record the concomitant medication;

(6) Record adverse events;

(7) Make an appointment for the next visit;

6.4 Follow-up 11 (Weks 52±5 days)

(1) Vital signs detection and physical examination;

(2) Disease assessment: PMR-AS score, pain VAS score, Patient self-assessment, Physician global assessment, morning stiffness time (min), difficulty in shoulder joint lifting (0, 1, 2, 3), difficulty in squatting and standing (0, 1, 2, 3, 4)

(3) Laboratory examination:

Blood routine: red blood cell count, hemoglobin, white blood cell count, platelet count, neutrophil count, lymphocyte count

Urine routine: urine protein, urine red blood cells, urine white blood cells

Liver function: ALT, AST, ALB

Renal function: BUN, CRE

Blood lipids: Total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides.

Blood glucose

CRP, ESR

(4) Bone mineral density;

(5) drug treatment;

(6) Record the concomitant medication;

(7) Record adverse events.

,Efficacy evaluations

7.1 The primary outcomes

The proportion of patients with remission at weeks 24.

7.2 The secondary outcomes

Proportion of patients in remission at weeks 52,

PMR-AS score, CRP, ESR at weeks 24;

Relapse rate, Relapse times, Cumulative dose of prednisone, Cumulative dose of MTX druing 52 weeks

7.3 Efficacy evaluations

PMR-AS<1.5且CRP<8 mg/L：

(1) It indicated remission

(2) Otherwise, it was thought as non-remission.

8. Safety

8.1 Adverse events

Record any unexpected or uncomfortable symptoms, signs, diseases, or the events which may lead to physical injury and was temporarily related to the drugs, but not necessarily causally related to the drug during the entire trial. It should be indicated that whether the adverse events were related to the investigational drug and whether they were related to polymyalgia rheumatica.

The possible adverse events include mild upper respiratory tract infection, mild urinary tract infection and herpes zoster. The corresponding treatment measures could be seen in the following part 10.12.

8.2 Lab test

During the study, laboratory tests were carried out as follows:

Blood routine: red blood cell count, hemoglobin, white blood cell count, platelet count, neutrophil count, lymphocyte count

Urine routine: urine protein, urine red blood cells, urine white blood cells

Liver function: ALT, AST, ALB

Renal function: BUN, CRE

Blood lipids: Total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides.

Blood glucose

Coagulation indicators: PT, APTT, FIB

The normal value range of relevant laboratory test items should be obtained before the study begins. If the patient had obvious abnormal laboratory test results after taking the drug, he should be followed up to the normal range (or return to the baseline state). If it failed to return to normal (or baseline) within a certain period, the investigator should conduct etiological examination and diagnosis.

9. Concomitant diseases and treatment

9.1 Concomitant diseases

Concomitant diseases were the diseases present at the time when the informed consent was given, and would be recorded on the case report form.

9.2 Treatment

All other treatments administered at the time when the subjects entered the study or at any time during the study were considered as concomitant treatment, and the drugs used were recorded in the case report form in the form of generic names. The concomitant medication during the trial period must be necessary for the subjects and the dosage should be kept at the lowest level when the investigators thought that there is no interference with the trial drug.

When the drugs for concomitant diseases had to be used during the trial period due to certain diseases, dosage should be monitored in addition to complying with the above principles.

9.3 Prohibited drugs

Subjects who using prohibited drugs or treatments at any time during the study would be judged as failure and excluded from the study. The following drugs and treatments are prohibited at any time during the study:

（1） Other investigational drugs (biologic or nonbiologic). Investigational drugs include any drug that is not approved for sale in the country but is in use;

（2） Another clinical study of an experimental drug at the same time or a clinical study of a non-drug treatment that might interfere with this study;

（3） Interleukin-6 (eg, Actemra),

（4） Other biologics (rituximab),

（5） Live vaccines are prohibited.

10. Handling of adverse event (AE) and serious adverse event (SAE)

It is the investigator's responsibility to discover and record events that meet the definitions of AE and SAE specified in the study protocol.

10.1 Definition of AE

An AE refers to any unfavorable medical event that occurs in a patient or clinical research subject using a certain drug, and it does not necessarily have a causal relationship with the treatment.

Therefore, an AE can be any unfavorable and unexpected sign (including abnormal laboratory test results of clinical significance), symptom or disease (new or exacerbation of pre-existing disease) temporarily associated with the drug; if marketed drugs should also include failure to produce the desired effect after use (that is, lack of effect), abuse and misuse.

Adverse reactions include:

（1）The test drug has good tolerance, and the incidence of adverse reactions is extremely low. If there is an allergic reaction, timely symptomatic treatment such as antihistamines or glucocorticoids can be given according to the general anti-allergic treatment method;

（2）Obvious or unforeseen aggravation or deterioration of the original disease;

（3）The exacerbation of the original chronic disease or the aggravation of the intermittent disease, manifested as an increase in frequency and/or intensity;

（4）The new disease is present or diagnosed after the use of the trial drug, even if it may have existed before the start of the study;

（5）Signs, symptoms or clinical sequelae arising from suspected interaction;

（6）Signs, symptoms or sequelae related to study drug overdose or other combined drug overdose (except for subject's own overdose);

（7） Reactions related to research drug allergy or toxicity;

（8） Obvious failure of expected pharmacological or biological response.

AE do not include:

（1）Medical or surgical examination and treatment process (such as endoscopy, appendectomy), but the disease that required these examinations is an AE;

（2）Circumstances where harmful medical events have not occurred (such as hospitalization for social accommodation or convenience of patients);

（3）Pre-existing diseases or conditions that existed or were discovered at the beginning of the study had expected periodic fluctuations, but did not worsen;

（4）The expected progression, symptoms, or signs associated with the disease or disorder, unless they are more severe than expected from the subject's disease.

10.2 Definition of SAE

A SAE is an AE that occurs at any dose level and meets any of the following conditions:

（1）cause death

（2）Threat to life

Note: Life-threatening means that the subject is in danger of death when the event occurs. This definition does not include events that could lead to death if the disease progresses further.

（3）Hospitalization or prolonged hospitalization

Note: In general, "inpatient" means that the subject is not suitable for observation or treatment in the outpatient or emergency department, but requires formal admission or emergency observation (usually at least overnight). Complications that occurred during hospitalization were considered AE. If the length of hospital stay was prolonged due to comorbidities or any other SAE criteria were met, it was also considered a SAE. Elective surgery performed because of a pre-existing condition that was not worse than baseline was not considered a SAE.

（4）Disability

Note: Disability refers to the substantial loss of a person's ability to live a normal life, excluding related minor illnesses such as simple headaches, nausea, vomiting, diarrhea, influenza, accidental injuries (such as ankle sprains), etc., although they There may be some impact on activities of daily living, but not substantial (long-term) loss.

（5）Congenital malformations/abnormalities

（6）Certain situations that require medical or scientific judgment to decide whether to report urgently in this situation: although not resulting in death, immediate life-threatening or hospitalization but may cause harm to the subject, or may require medical or surgical treatment to prevent an important medical event that occurs as a result of one of the consequences listed above can be considered a SAE. Such medical events included invasive or malignant cancer, allergic bronchospasm requiring intensive care in the emergency room or at home, haematological dyscrasias or convulsions that did not result in hospitalization, and events of drug dependence or abuse.

10.3 Lack of efficacy

Lack of efficacy itself cannot be reported as an AE, and any symptoms/signs or sequelae caused by lack of efficacy need to be reported only if they meet the criteria for AE/SAE.

10.4 Abnormal clinical test results

Some abnormal laboratory results (such as clinical biochemistry, hematology, urinalysis) or other abnormal indicators (such as electrocardiogram, vital signs, etc.) are judged by the investigator to have clinical significance, if they meet the definition of AE in section 10.1 ("Definition of AE"), or the definition of a SAE in Section 10.2 ("Definition of SAE"), it must be recorded as an AE or as a SAE. Clinically significant abnormal laboratory test results and other abnormal findings that are found after treatment, or exist at the baseline assessment and aggravate after the start of the study, should be regarded as AE or SAE. However, clinically significant abnormal laboratory test results or other abnormal findings related to the disease under study are not included in AE or SAE unless the investigator determines that the subject's condition is more serious than expected. Abnormal laboratory results or other abnormal findings that existed or were detected but not exacerbated at the beginning of the study were also not

included in AE and SAE.

It is up to the investigator to determine whether an abnormal laboratory test result or other abnormal finding is clinically significant.

10.5 How to find AE

AE will be informed through oral questions and recorded on the case report form (CRF). Investigators or designees should use the same questions each time they ask about AE to avoid inter-subject variability. Researchers can ask:

"Have you felt any different since your last visit?"

In response to the subjects' answers to the above questions, the researcher can ask some related questions according to the patient's special complaints, such as:

How severe are the symptoms?

How often does it appear?

How long do general symptoms last?

Investigators also asked subjects about past unresolved AE. The investigator will assess the intensity, severity, relationship to the trial drug, and management of AE.

From before the start of the experiment to the end of the experiment or the corresponding exit visit, the researcher will ask the subjects the above questions.

10.6 Records of AE and SAE

When an AE/SAE occurs, the investigator is responsible for reviewing all relevant records (such as disease course, laboratory examinations, and diagnostic reports), and recording the information related to the event in the subject's case report form.

When recording adverse reactions, it should be indicated whether the adverse reactions are related to the test drug; and whether they are related to PMR. Researchers should try their best to judge the event based on symptoms, signs and/or other clinical data. In such cases, the diagnosis should be recorded as an AE and/or SAE rather than a subject's signs/symptoms.

10.7 Assessment of AE and SAE

10.7.1 Judgment of severity

During the study period, investigators should use their own clinical judgment to assess the severity of each AE and SAE reported. AE and SAE recorded in the case

report form should be classified according to the following criteria:

Mild: events that only cause slight discomfort to the subject, do not affect daily activities, and are relatively easily tolerated by the subject;

Moderate: Events that cause significant discomfort to the subject and interfere with normal daily activities;

Severe: Events leading to inability to perform normal daily activities.

Be careful not to confuse severe AE with SAE: Severity is a category used to measure the severity of events. Both AE and SAE can be rated as severe. SAE should be included.

10.7.2 Judgment of causality

Researchers must judge the relationship between each AE/SAE and the drug based on clinical experience. The relationship between the AE and the trial drug was evaluated according to five levels: definitely related to the drug, probably related, possibly related, probably irrelevant, and irrelevant.

（1）Definitely related: the time sequence of medication and reaction is reasonable; After withdrawal of the drug, reaction stops, or quickly alleviates or improves; the reaction reappears after repeated use; it is also supported by literature; and the influence of other confounding factors such as the original disease has been excluded;

（2）It is likely to be related: no history of repeated medication, the rest is the same as "definite" or although there is a combination of medication, the possibility of the reaction caused by the combination of medication can be basically ruled out;

（3）Possibly related: There is a close relationship between the medication and the time of the reaction, as evidenced by literature; however, there are more than one drug causing the adverse reaction, or the disease progression factors of the original disease cannot be excluded;

（4）Possibly irrelevant: the adverse reaction is not closely related to the time of medication, and the reaction performance does not match the known adverse reactions of the drug.

The development of the original disease may also have similar clinical manifestations;

（5）Irrelevance: There is no relationship between adverse reactions and medication time.

Adverse reactions refer to the sum of 1, 2, and 3.

Other causes, such as the natural history of the underlying disease, other concomitant treatments, risk factors, and events temporally related to the trial drug, should be considered, and examined. Investigators should also consult the clinical investigator's brochure and/or the relevant information of the trial drug (if it is a commercially available drug) for evaluation.

Investigators may have little information when initially reporting a SAE, however, it is important for investigators to assess causality of each event before reporting escalation to the CRF for SAE. The researcher can change the judgment of causality according to the visit data and modify the corresponding CRF page accordingly. The judgment of causality is one of the necessary indicators.

The investigator should provide a causality assessment in the format of the SAE table in the CRF.

10.8 Visits for AE and SAE

Once an AE/SAE is reported, the investigator should visit each subject. All AE/SAE that have been recorded and persisted in the previous visit/re-visit should be re-examined in this visit/re-visit.

All AE/SAE must be followed up until their remission, stable condition, other explanations for the cause of the event, or loss of subjects. Once the issue is resolved, the AE/SAE section of the CRF should be updated in a timely manner. The investigator may add additional tests to the visit that may help clarify the nature and/or cause of the AE or SAE. This may include additional laboratory tests or studies, pathology tests, or consultation with other professionals.

New or updated information should be recorded on the initially completed CRF SAE page, and the investigator should sign and date the new or updated information.

10.9 Management and Reporting of SAE

Once the investigator finds that a SAE has occurred in the subject, he must take immediate action. The SAE report form should record all available event-related information as completely and in detail as possible. In the initial report, the investigator should evaluate the causality according to 10.7.2 (judgment of causality), and report to the ethics committee.

The relevant information about the ethics committee is as follows: Clinical

Research Ethics Committee, Ethics Secretary, located at No. 79 Qingchun Road, Shangcheng District, Hangzhou City, Zhejiang Province, telephone number 0571-87233418.

SAEs must be reported to the project principal investigator and the ethics committee within 24 hours of discovery, and SAE reports should be completed in accordance with hospital regulations. The research team should continue follow-up until the event resolves, stabilizes, or reaches a definitive outcome.

10.10 AE and SAE after the end of study

AE/SAE after the end of the study refer to any events that occur outside the visit period specified in 10.5. Researchers do not have to actively seek out AE and SAE that occurred in subjects who have completed clinical research and visits. However, if the investigator becomes aware of any SAE (including death) at any time after a subject has been withdrawn from the study, and the event is likely to be related to the study drug, the investigator should contact the subject and deal with it accordingly, make corresponding records, and report to the ethics committee.

10.11 AE and SAE related to trial

SAEs are related to participating in the study (such as operations, invasive examinations, and changes in existing treatment regimens), whether they occur before or after treatment, should be dealt with and recorded in time, and reported to the ethics committee.

10.12 Treatment for AE in this trial

1. Abnormal blood routine and liver function:

	Continue the original plan and give symptomatic treatment	Decrease dose of Ivarmacitinib and give symptomatic treatment	Stop Ivarmacitinib
Blood routine	WBC $\geq 3\times10^9$/L	3×10^9/L>WBC>2.5×10^9/L	WBC<2.5×10^9/L
Liver function	Transaminases elevated < 1.5-fold	1.5-fold ≤ Transaminases elevated < 3-fold	Transaminases elevated ≥ 3-fold

In the above situation, hepatoprotective drugs and agents for leucopenia can be added as appropriate. Researchers need to adjust the treatment regimen according to the

correlation between adverse events and drugs. If the re-examination of liver function is normal, the original therapeutic dose can be restored; if abnormal liver function occurs again, the dose should not be increased after the dose is reduced/stopped. The trial drug was discontinued for 8 consecutive weeks, and the patient withdrew from the study.

2. Drug allergy: withdraw from the study and treat according to clinical experience.

3. Mild upper respiratory tract infection, mild urinary tract infection, herpes zoster and other AE: They should be diagnosed and treated according to clinical diagnosis and treatment routines. It is controllable and treatable.

If SAE occur, they should be withdrawn from the trial.

10.13 Principles of drug suspension, resumption and termination of treatment

To ensure the safety of the subjects, if any of the following situations occur during the research period, the study drug treatment can be suspended or terminated based on the judgment of the investigator.

(1) Suspension of study drug treatment

If any of the following situations occur, emabetastine treatment should be suspended:

① Active infection, including but not limited to pneumonia, herpes zoster, cellulitis, severe urinary tract infection, sepsis, etc.; ② ALT or AST ⩾ 5 times the upper limit of normal value (ULN); ③ Absolute neutrophil count (ANC) < 1.0×10^9/L; ④ Lymphocytes < 0.5×10^9/L; ⑤ Hemoglobin < 80 g/L; ⑥ Other situations that the investigator considers may increase the risk for the subject if continued treatment is continued.

(2) Conditions for resuming study drug treatment

When the following conditions are met simultaneously, emabetastine treatment can be resumed:

① Infection has been completely controlled; ② Laboratory indicators have returned to the allowable range; ③ The investigator comprehensively judges that the benefits of continued treatment outweigh the risks; ④ The subject has given informed

consent to continue participating in the study.

(3) Permanent termination of study drug treatment

If any of the following situations occur, the study drug should be permanently stopped:

① Severe opportunistic infection; ② Active tuberculosis; ③ Deep vein thrombosis (DVT) or pulmonary embolism; ④ New-onset malignant tumor; ⑤ Severe allergic reaction or drug hypersensitivity reaction; ⑥ Repeated severe laboratory abnormalities that cannot be restored after adjustment; ⑦The investigator considers that continued treatment poses a significant risk.

After stopping the study drug, safety follow-up should continue until the end of the study or the subject withdraws from the study.

11. Drugs adherence

After the trial, we will evaluate the adherence of the patient, record the doses of drugs used, and record whether the patient uses the trial drug.

12. Withdrawal

12.1 Subject completes the trial

Subjects are considered to complete the trial when they have completed all elements specified in each scheduled visit in accordance with the requirements of the trial.

12.2 Subject withdraws from trial

Any subject who entered the trial (signed informed consent) failed to complete the experiment in accordance with the requirements of the above definition for any reason, and would be considered an withdraw from trial, regardless of whether they used the trial drug.

144 patients are expected to be selected randomly, and the subjects participating in the trial will get the unique random number.

Each subject can withdraw from the study at any stage, any reasons (special or non-special) without being discriminated against. The treatment of patients will not be restricted. Under appropriate cases, the researchers will use conventional treatment

methods to treat patients.

Patients who withdraw should be visited as much as possible. Patients who withdraw after randomization should complete the current visit if they withdraw at the time of the scheduled visit. All subjects who withdraw from the trial after randomization should complete all the evaluations required by the visit 3.

The case report forms of all the subjects participating in the randomization must be filled in completely, and the reasons for all withdraw subjects who were randomized but did not complete the trial should be recorded on the "trial summary" of the case report form. In addition, the date of last dose for subjects who withdrew from the trial must be recorded on the "trial completion summary".

12.3 Screening and baseline assessment failure

Patients withdraw from the trial prior to randomization are considered screening failures. The reason for withdrawing from the trial should be recorded in the patient screening entry form.

13. Data management

（1）Researchers should carry data based on the subject's original observation records in time, completely, correctly, and clearly into the case report form.

（2）Confirm that the report forms of all cases are filled in correct and completely, and consistent with the original information. If there are errors and omissions, the researchers are required to correct them in time. When modified, the original record must be clearly visible, and the correction must be signed by the researcher and indicated the date.

（3）There should be a special record for the transmission of the complete case report form between researchers and data manager. When a record is received, there should be a signature, and the record needs to be properly maintained.

（4）Data manager should check again before the data entry, promptly notify the researcher of any problems and request answers from the researcher. The exchanges of questions and answers between researchers should be used in the form of question tables, and the question table should be preserved properly.

（5）Before data entry, date mangers must understand the content and coding of each item of the observation form, and record the encoding work process to the coding book for preservation. Database naming should be standardized, easy to read, and

easy to find. And ensure that it is correct, safe and confidential.

（6）The data entry clerk enters data using secondary entry. Problems or unexpected situations found in the data entry process should be registered and reported in time so that the problems can be dealt with quickly. After the data entry is finished, some observation forms should be sampled to understand the quality of the entry and analyze and deal with any problems.

（7）Data mangers shall, together with the main researchers, formulate data range inspection and logical inspection content according to the scope of each indicator value and relationship in the report form in the case. And write the corresponding computer program, control the error data input before the input, and find out the reason for the error to correct it. All error content and modification results should be recorded and preserved properly.

（8）The original case report form, after completing data entry and verification as required, is archived and kept in a numbered order with a searchable table of contents, etc., filled in for reference. Electronic data files include databases, inspection procedures, analysis procedures, analysis results, encoding books, and explanation files. They should be categorized and stored, and multiple backups are stored on different disks or recording medias to properly store and prevent from damage. All original archives should be stored in accordance with the prescribed period of Chinese "Good Clinical Practice" .

14. Statistical analysis

Finalize statistical analysis according to data characteristics. This plan provides statistical conventional requirements.

14.1 Sample size determination

According to perspective of effectiveness and the statistical requirements, the differential test is adopted, and the two-sided test is used α=0.05, β = 0.10 (90% confidence). The remission rate at 24 weeks is the primary endpoint, and the remission rate of the patients in the experimental group is predicted. The remission rate in experimental group was 90%, the remission rate of the control group was 90%, the margin of superiority/non-inferiority was 0.16, the sample distribution ratio of the two groups was 1:1, calculated by http://www.powerandsamplesize.com/Calculators/, 56

cases are needed in each group.

Given the potential increase in Type I error rate caused by interim analysis, with an overall Type I error rate (α) of 0.05, we will adjust the p-value threshold. The significance threshold for the interim analysis is set at $p<0.025$, and the final analysis's significance threshold is also set at $p<0.025$, keeping the combined α at 0.05. Therefore, the sample size needs to be recalculated, with 65 cases in each group, and considering a dropout rate of 10%, at least 72 cases are needed in each group. The minimum effective total sample size is 144 cases, with the final experimental and control groups each consisting of 72 cases.

14.2 Analysis set

14.2.1Analysis set in this study

(1) Full Analysis Set (FAS): It is established based on the ITT (Intention-to-Treat) principle, including all subjects who completed the random grouping and received at least one treatment of the study. The main efficacy analysis is conducted using FAS.

（2）Per-Protocol Set (PPS)：This refers to the collection of cases that met the inclusion criteria, did not meet the exclusion criteria, and completed the treatment protocol, i.e., Cases that met the trial protocol, had good compliance, and completed the required completion of the CRF were analyzed (PP analysis). PP analysis was mainly used for the main efficacy indicators.

（3）Safety Set (SS)：At least one treatment is received, and actual data recorded by security indicators. Safety missing values were not allowed to be carried forward. We include partially excluded cases for evaluation, such as those older than the inclusion criteria, but not those in which the use of prohibited drugs rendered a safety determination impossible. The incidence of adverse reactions was determined using the number of cases in the safety set as the denominator.

14.2.2 Missing Data Handling

For the primary outcome, multiple imputation was performed to address missing data. To assess the robustness of the primary findings, last observation carried forward was utilized as a sensitivity analysis. Continuous secondary variables with missing values were analyzed without artificial imputation. Missing safety data were not imputed and were summarized using available case analysis.

14.3 Statistical Methods

14.3.1 Patient enrollment analysis

- List the overall selection and complete cases, and determine the three analysis data sets (FAS、PPS、SS).
- List the cases and reasons for falling-off and exclusion.

14.3.2 Population data and baseline analysis

Descriptive statistics demographic information and other baseline characteristic values：

- Continuous variables calculate the cases, mean, standard deviation, median, minimum, and maximum values.
- Calculation and grade data count frequency and constituent ratio.
- Inference statistical results (*P* value) are listed as descriptive results.

14.3.3 Efficacy analysis

Efficacy analysis

- The comparison of the proportion and relapse rate of patients with remission at 24 and 52 weeks of treatment was analyzed between two groups by Fisher's exact test.
- After measuring values of PMR-AS scores, CRP, and ESR at 24 weeks of treatment, the number of recurrences within 52 weeks, and the cumulative doses of hormones and MTX within 52 weeks, we compare differences between two groups using repeated ANOVA.

14.4 Safety analyses

- Calculate the incidence of adverse events and adverse reactions;
- Calculate the incidence of serious adverse events;
- Frequency and relative frequency of adverse events and reactions are in the subsystem and percentages are calculated, then analyzed by Fisher exact test;
- List the detailed list of adverse events;
- List the detailed list of adverse reactions
- Laboratory inspections, electrocardiogram, and physical examinations of "normal transition" or "abnormal intensification" after trial;
- List laboratory examination, electrocardiogram, physical examination abnormal cases and clinical interpretations
-

14.5 Statistical software

- Analysis using SPSS 18 software
- All statistical tests were performed using bilateral test, and a p-value less than or equal to 0.05 would be considered statistically significant for the difference tested
- The detailed statistical method will be provided in the statistical analysis plan.

14.6 Interim analysis

The interim analysis will evaluate the preliminary efficacy and safety of the Ivarmacitinib combined with prednison induction tapering regimen for PMR. Most subjects will undergo the interim analysis at 16 weeks of follow-up, evaluating and monitoring the progress of the clinical trial, subject recruitment, and screening, as well as data collection and analysis, to ensure the progress and quality of the trial.

Interim analysis plan:

Time point: The majority (70%) of subjects have completed the 16-week follow-up and an interim analysis will be conducted.

Method: Baseline demographic and clinical characteristics of the study participants, including age, gender, baseline disease activity scores, and relevant data within 16 weeks, will be collected. Adverse events, severe adverse events, and concomitant medication use throughout the entire study will be recorded.

Efficacy outcomes: PMR-AS score for disease activity, CRP, and ESR, will be evaluated at baseline and at weeks 16.

Based on the observed treatment effects and statistical results of the interim analysis, if $p<0.05$ suggests that the treatment group is superior to the control group in terms of efficacy, the study will continue. If $p>0.05$ indicates no statistical difference in the results between the treatment and control groups, but the safety profile of the treatment group is superior to the control group, the study may continue. However, if $p>0.05$ and the safety profile of the treatment group is not superior to the control group, the study will be stopped.

15. Research management

15.1 Comply with GCP requirements

This trial shall be performed in accordance with the requirements of the Chinese

Good Clinical Practice.

15.2 Privacy of subjects

When filling in and managing the report form, the privacy of the patient should be considered, such as the patient's random number to represent the patient, etc. The patient's initials may also be used as a surrogate for his or her name

15.3 Informed consent

Prior to starting this trial, we must explain the content in subject's informed consent to each participant that can easily understand. Then we obtain written informed consent from the patient to voluntarily participate in this trial. Enter the date written informed consent was obtained in the CRF.

（1）Nature and purpose of the research;

（2）Research process

（3）Benefit and risk

（4）Other alternative treatment

（5）The right to subject: Patients refuse to participate in this trial at any time, they can withdraw from this trial, and the patient's rights will not be affected by any way.

（6）Confidentiality agreement

（7）What the patient must follow

（8）And any matters believed to protect the rights of the patient

15.4 Protocol revision procedure

When the plan must be modified or suspended in this trial, the principal researchers should immediately notify all personnel participating in the trial. In the case of major modifications, new ethics committee approval should be obtained before implementing.

15.5 Case report form recording and modification procedures

True and accurate recording of trial data.

If you need to make any modifications, please keep the record of modification legible, and sign the date. If the scope of the amendment is large or the changes are significant, the modified person should indicate the reason for the revision and modification, and sign it at the same time.

15.6 Quality Control

（1）Adopting standard operating procedures ensure the quality control of study and quality assurance systems for this clinical trial.

（2）All observed results and abnormalities findings in clinical trials should be carefully verified and recorded in time to ensure the reliability of data. Various instruments, equipment, reagents, standard products, etc. used in various inspection items in clinical trials should have strict quality standards and ensure that they work in normal state. The records and metastasis of clinical data must be responsible for experienced physicians, and special persons supervise or verify to ensure the scientific and accuracy of the data. Various conclusions of clinical trials must be derived from the original data.

（3）Doctors responsible for the test should fill in the CRF in a complete, detailed, accurate, and timely manner. After the signature of the hand -to senior physician is confirmed, it is submitted or saved in accordance with the prescribed procedures. All data related to the trial should be centralized and analyzed.

（4）Establish procedures for data storage, data transmission, and data query. The custody information includes: the subject's research medical records, imaging materials, CRF, pharmaceutical registration form, subject screening form, subject recognition code table, serious adverse event report forms, GCP forms required to fill in each hospital, visit report form and various original medical documents. The passed data includes: the subject random table, CRF, serious adverse event report forms and data and information to be used in summarizing information.

（5）When we sum up and analyze the results of clinical trials, standardized statistical analysis methods must be adopted, and those who are familiar with biological statistics must be invited to participate.

15.7 Data storage

（1）The original data is kept by the research institution.

（2）Retention period until 5 years after the end of the study.

（3）All information of this clinical trial belongs to the First affiliated hospital,

Zhejiang University school of medicine.

15.8 Schedule

Because of the low prevalence of the disease, the duration of the study was set at 2 years to collect the full number of patients

15.9 Conflict of Interest

This is an investigator-initiated trial. The study design, participant recruitment, data management, statistical analysis, manuscript drafting, and publication were conducted independently by the research team without involvement from any pharmaceutical companies. The authors declare no conflicts of interest related to this study. Any drug donations or research funding received were utilized solely to alleviate the financial burden on participants and support trial execution, with no influence on the study design, data analysis, interpretation of results, or decision to publish.

16. Paper publication

The researchers and other staff of the research center shall keep confidential all information provided by the First Affiliated Hospital of Zhejiang University School of Medicine and all data generated by the center of the research during the course of the study (except medical records of the subjects). Researchers or other staff of the research center may not use the information, data, or records for any purpose other than for the purpose of this study. These restrictions do not apply to information that: (1) has been made publicly available through no error on the part of the investigator or staff; (2) must be disclosed for the purpose of gaining the confidence of an academic or ethics committee to evaluate the study; or (3) must be disclosed in order to provide appropriate health care to the subjects participating in the study.

17. References

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Table 1 2012 EULAR/ACR Classification Criteria for PMR

Required Criteria:	age＞ 50 years，bilateral shoulder aching, abnormal ESR/CRP

	Points Without Ultrasonography （0-6）	Points With Ultrasonography （0-8）
Morning stiffness duration＞ 45 min	2	2
Hip pain or limited range of movement	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
≥1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and ≥1 hip with synovitis and/or trochanteric bursitis	/	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	/	1

A score ≥4 without ultrasonography is categorized as PMR, and a score ≥5 with ultrasonographic finding is categorized as PMR.

Table 2 Polymyalgia rheumatica disease activity score (PMR-AS)

CRP (mg/dl)	
Patient self-evaluation (0-10 visual scale) 0=no pain, 10=no pain tolerable	
Physician global assessment (0-10 Visual Scale) 0=no pain, 10=no pain tolerable	
Morning stiffness time min x0.1	
Shoulder joints（0-3） 0=lifted above the shoulder girdle, 1=to the shoulder girdle, 2=below the shoulder girdle, 3=cannot lift	
Total	

PMR-AS score= CRP (mg/dl)+ Patient self-evaluation（0-10）+ Physician global assessment（0-10）+ Morning stiffness min x0.1+ Shoulder joints（0-3）

Table 3 Squat and stand-up assessment in PMR

Difficulty squatting and standing due to hip muscle involvement, score 0-4

Squatting: 0 = No difficulty, 1 = Can squat with the help of others or upper body strength, 2 = Cannot squat even with the help of others or upper body strength.

Standing up: 0 = No difficulty, 1 = Can stand up with the help of others or upper body strength, 2 = Cannot stand up even with the help of others or upper body strength.

For example, no difficulty in squatting and standing up: 0 points; cannot complete squatting and standing up with the help of others or upper body strength: 4 points.