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Randomised, double-blind, multicentre, phase I/II dose escalation and expansion trial of GR1501 in patients with plaque psoriasis: study protocol

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ABSTRACT

Introduction Psoriasis is a life-long, immune-mediated disease that greatly reduces the quality of life of patients. Plaque psoriasis is the most common form of psoriasis. Treatment options for plaque psoriasis with good tolerance and sufficient response remain profoundly limited. Based on mechanistic findings that suggest the key pathogenic role of interleukin (IL)-17 in plaque psoriasis, we hypothesise that GR1501, a new monoclonal antibody (IL-17A targeted), will be an efficacious treatment for plaque psoriasis. This phase I/II trial aims to evaluate the safety, tolerability, pharmacokinetics, immunogenicity and preliminary efficacy of GR1501.

Methods and analysis A multicentre, randomised, double-blind, phase I/II dose escalation and expansion trial will be conducted at four hospitals in China. In total, 226 patients with plaque psoriasis will be enrolled in the study, with 46 cases in the dose-escalation stage and 180 cases randomised to GR1501 or the placebo in a 3:1 ratio in the expansion cohort. The primary outcomes are safety and tolerability; the secondary outcomes include pharmacokinetics, immunogenicity and efficacy.

Ethics and dissemination The study is in accordance with the Declaration of Helsinki, and the ethics approvals of the protocol have been obtained from the ethics committees of all participating centres, including Peking University People's Hospital, Chinese PLA General Hospital, The First Affiliated Hospital, College of Medicine, Zhejiang University and the Second Xiangya Hospital of Central South University. The findings of the study will be presented in published journals or at scientific conferences or meetings.

Trial registration number ChiCTR1800017956.

Strengths and limitations of this study

- In this study, we will use the combination design of phase I/II dose escalation and expansion, an innovative study design, which is intended to accelerate the development of new drugs from bench to bedside by seamlessly proceeding from the initial determination of a potentially effective dose in subject cohorts using the phase IIb trial approach.
- Choosing no observed adverse effect level as the method of determining the starting dose may lead to the inability to account for the effect of pharmacological pathways on dose selection.
- The inclusion of seriously ill patients or those with concomitant diseases and medications as study subjects may bring potential risks.

INTRODUCTION

Psoriasis is a common life-long immune-mediated genetic disease characterised by raised areas of abnormal skin and/or joint symptoms, with a prevalence of 2%–4%.[1 2] Plaque psoriasis is the most common type of psoriasis, accounting for approximately 90% of all psoriasis cases.[1] Patients with psoriasis report a tremendous economic and psychosocial burden, with tens of thousands of dollars being spent annually on the disease and a significant reduction in physical activity, cognitive function and quality of life.[3 4] Psoriasis results from a T-cell-mediated immune inflammatory response, which is mainly driven by the TNF-α pathway and interleukin-23 (IL-23)/Th17/IL-17 axis pathway. In the IL-23/Th17/IL-17 axis pathway, progression of psoriasis leads to an increase in the level of IL-23, which then drives the differentiation of Th17 cells. Activated Th17 cells produce several mediators such as IL-17A, which induces keratinocyte proliferation and other hallmark features of psoriasis.[5–8] IL-17A is a proinflammatory cytokine mainly produced by activated T cells. Many studies have shown that IL-17A plays an important role in the pathogenesis of various inflammatory diseases: plaque psoriasis, ankylosing spondylitis and rheumatoid arthritis.[9 10]

Currently, the available treatments for patients with psoriasis include phototherapy, traditional systemic therapy and targeted

biologics.[11] The management of plaque psoriasis has been revolutionised in the past decades with the advent of biologic agents owing to their high efficacy and tolerability.[12] Anti-IL-17 agents are one of the most efficacious biologic agents available for psoriasis. Currently, there are three anti-IL-17 agents on the market: secukinumab, ixekizumab and brodalumab.

GR1501, a fully human IgG4 monoclonal antibody, is a new product targeted at IL-17A with high affinity and selectivity for IL-17A; it is to be administered subcutaneously. The objective of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity and preliminary efficacy of GR1501 via a phase I/II dose escalation and expansion clinical trial of GR1501 in patients with moderate to severe plaque psoriasis. The study will provide baseline data for the next phase of clinical trials.

The study protocol consists of two stages: the dose-escalation stage and the expansion cohort stage. In the dose-escalation stage, the primary outcome is the safety and tolerability of GR1501. The secondary outcome includes the PK characteristics, immunogenicity and efficacy of GR1501 after single or multiple subcutaneous injections. The expansion cohort will help obtain more reliable outcomes for safety and tolerability as well as toxicity estimates and efficacy outcomes in a larger population.

METHODS AND ANALYSIS

Study design

This is a randomised, double-blind, multicentre, phase I/II dose escalation and expansion trial in China, aiming to evaluate the safety, tolerability, immunogenicity, PK and efficacy of GR1501 in patients with moderate to severe plaque psoriasis. In the phase I/II trial, 46 patients will be enrolled in the dose escalation cohorts who will receive dose from 10 to 200 mg with single-ascending dosing (SAD) and multiple ascending dosing (MAD). The study will also have 180 patients enrolled in the expansion cohort, who will receive the following doses: 100, 150 and 200 mg.

Preclinical data (unpublished data)

Preclinical studies have demonstrated that there is a linear correlation between the drug concentration and time after a single dose of 3, 10 or 30 mg/kg of GR1501 in cynomolgus monkeys. There was no statistically significant difference in the time to reach the peak concentration in serum (T_{max}) and half-life ($t_{1/2}$) for multiple doses (10 mg/kg, once a week, four times in a row) when compared with the same dose on single administration. However, the peak concentration in serum (C_{max}) and the drug exposure level were higher with multiple doses. The accumulation index after continuous administration was 4.03±1.46. The absolute bioavailability was 0.77. GR1501 was mainly excreted through the urine. There were mainly drug prototypes in the serum and small molecular metabolites in the urine. Drugs and their metabolites could not easily cross the blood–brain barrier.

A preclinical toxicity trial showed that in the range of 35–400 mg/kg dose, there was no obvious toxicity after a single subcutaneous injection of GR1501 in cynomolgus monkeys, and the maximum tolerated dose (MTD) was ≥400 mg/kg. There was no obvious related toxic reaction and local irritation after an escalating dose of 15, 50 and 150 mg/kg for 13 weeks (once a week for a total of 14 times), followed by drug withdrawal for 6 weeks in cynomolgus monkeys. The no observed adverse effect level (NOAEL) was 150 mg/kg. In other preclinical studies, haemolysis and coagulation, local irritation and positive antidrug antibody cases were not observed in cynomolgus monkeys.

Dosing rationale

The starting dose is based on three aspects. First, referring to the NOAELs in the tested animal species, converting NOAELs to human equivalent dose, and selecting the most appropriate animal species, the starting dose should be 364 mg based on safety considerations. Second, referring to the 1/10 clinical dose of drugs with the same pharmacological target, secukinumab and ixekizumab, the starting dose should be 15 mg or 30 mg and 8 mg or 16 mg, respectively. Third, the starting doses of secukinumab and ixekizumab in the dose-escalation trial were 0.3 $mg \cdot kg^{-1}$ and 5 mg, respectively. In summary, the starting dose of GR1501 will be 10 mg based on the formulation specifications and our preclinical data.

The MTD for humans is based on the 1/5–1/2 principle of the MTD for long-toxicity tests in animals. The MTD can be considered to be greater than 1800 mg, based on a healthy per capita weight of 60 kg. Considering the clinical doses of secukinumab and ixekizumab and according to the preclinical study results, the product is expected to be well tolerated; thus, the MTD is tentatively set at 200 mg. In summary, according to a modified Fibonacci sequence and the determined starting dose and maximum tolerable dose, the doses in the dose-escalation stage will be 10, 30, 60, 100, 150 and 200 mg.

Dose escalation

The patients will first receive a single dose and will be observed for 6 weeks (SAD). Then, the patients in the 60–150 mg dose group will continue to receive 12 weeks of consecutive multiple doses (MAD) once every 2 weeks. They will also be observed for 10 weeks after the 12-week administration. A single dose of the next dose group will be started on the premise that a single dose of the previous dose group is safely tolerated (single dose observation for at least 2 weeks) in half of the patients. Multiple doses of the previous dose group for 12 consecutive weeks will be started on the premise that a single dose of the next dose group is safely tolerated (single dose observation for at least 2 weeks) in half of the patients. Refer to figure 1 for details.

Group	1	2	3	4	5	6
Increasing proportion	Starting dose	200	100	66.7	50	33.3
Administration dose	10	30	60	100	150	200
Administr ation cycle	Single dose	Single dose	Single dose+Q2W	Single dose+Q2W	Single dose+Q2W	Single dose
Number of cases in the trial group	2	2	9	9	9	9
Number of cases in the placebo group	1	1	1	1	1	1

Figure 1 Schematic overview of the dose-escalation stage.

Expansion cohort

A randomised, double-blind, placebo-parallel, multicentre study in the expansion cohort will be conducted after the dose-escalation study. One hundred and eighty patients will be randomly divided into the 100 mg arm, 150 mg arm, 200 mg arm and placebo arm in a ratio of 1:1:1:1 and administrated the drug for 12 consecutive weeks (multiple-dose period). At the 12th week, the patients in the active arm with effective outcomes (effective: relative baseline Psoriasis Area and Severity Index (PASI) score reduction ≥75%; partially effective: relative baseline PASI score reduction ≥50% but<75%; ineffective: relative baseline PASI score reduction <50%) will be randomly assigned to the 200 mg Q4W arm and 200 mg Q12W arm in a ratio of 2:1; they will thus enter the long-term dose administration period for 40 weeks. At week 12, the patients in the placebo arm and those in the active arm who have partially effective and ineffective outcomes will receive 200 mg Q4W for 40 consecutive weeks. There will be a 4-week follow-up after the end of the long-term dose administration period (follow-up period) after a total of 52 weeks of administration. Refer to figure 2 for details.

Criteria for the discontinuation of study treatment

In the dose-escalation stage, the investigator will stop the study if one or more patients in the test group experience grade 3 or higher adverse events related to the study drug, if half or more patients in the test group experience grade 2 adverse events related to the study drug, or when the maximum dose is reached. In addition, the sponsor, the administrative department or the ethics committee may discontinue the study if necessary. In the expansion cohort, if one or more patients in the 200 mg group experience grade 3 or higher adverse events related to the study drug at any time point or if half or more patients in the 200 mg group experience grade 2 adverse events associated with the study drug at any time point, the data safety supervisory committee will hold a meeting to review case information, assess risks and make suitable recommendations (eg, termination, suspension and continuation).

Study population

Adults (18–65 years old) with a diagnosis of chronic stable plaque psoriasis will be enrolled. Patients with other types of psoriasis or patients who have recently received relevant treatments or drugs will be excluded from the study. In the course of the study, patients will be withdrawn from the study if at least one of the following occurs: poor compliance to medicines, other coadministered drugs or

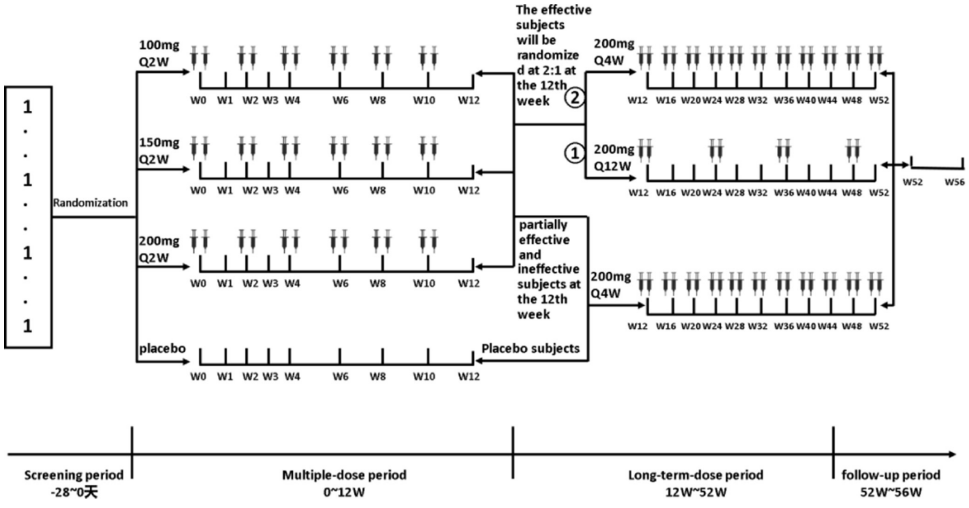

Figure 2 Schematic overview of the expansion cohort.

foods affect the study drug tolerance judgement and drug metabolism process, voluntary withdrawal from the study, occurrence of serious adverse events whose causality cannot be determined by the investigator, the investigator determines that the treatment is invalid or it is otherwise inappropriate to continue the trial. The inclusion and exclusion criteria are detailed in the online supplemental appendix 1.

Randomisation and blinding

Randomisation and blinding will be performed by an independent investigator who will not be involved in the data management and statistical analysis of the trial. The DAS electronic interactive web response system (DAS for IWRS) will be used to generate randomisation codes and allocate treatments. Randomisation will be performed using the SAS (V.9.4) software. The expansion cohort will be established using a dynamic randomised method, considering body weight (≥75 or <75 kg), use of biological agents for plaque psoriasis (yes or no) and static physicians global assessment (sPGA) score (3≤sPGA < 4 or sPGA ≥4).

The patients will be allocated a numbered treatment pack, which will contain all the drugs or placebos needed to complete a course of the trial treatment. All trial drugs will be packaged identically and identified only by numbers. Patients, investigators and study site personnel will remain blinded to the randomisation codes until the end of the trial.

Accidental unblinding of the study participants will be informed and explained to the clinical trial unit leader, clinical research associate and trial statistician within 24 hours. All identified unblinded cases before the end of the trial will be considered drop-out cases, and such data will be kept intact.

Combination therapy

In the course of the study, the use of systemic and topical treatments for psoriasis will not be permitted. These include methotrexate, cyclosporine, etretinate, hormones and phototherapy.

The drugs permitted to be used by the study participants in the course of the study include hypolipidemic drugs, antihypertensive drugs, antidepressants, oral type II insulin drugs, oestrogen replacement therapy, antihistamines for pruritus, antacids, non-steroidal anti-inflammatory drugs, histamine H_2 receptor antagonists, proton pump inhibitors, calcium supplements and topical ophthalmic drugs. Moreover, the study participants will be permitted to use topical antibiotics (for secondary infections), tar-containing shampoos, paracetamol or aspirin, topical moisturisers/emollients (not containing urea, hormones), bath oils and salicylates. The participants will be required to consult the investigator when using any other drugs or dietary supplements.

Evaluation criteria for outcome

The safety and tolerability evaluation criteria will include adverse events (the severity of the adverse events will be graded according to the Common Terminology Criteria for Adverse Events V.4.0. online supplemental appendix 2), laboratory tests, vital signs and physical examinations. The PK evaluation criteria will include C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, T_{max}, $t_{1/2z}$, V_z, CL_z, λ_z, $MRT_{0\text{-}t}$, $MRT_{0\text{-}\infty}$ and $AUC_{\_\%Extrap}$ in SAD and $C_{max,ss}$, $AUC_{0\text{-}t,ss}$, $AUC_{0\text{-}\infty,ss}$, AUC_{ss}, C_{av}, T_{max}, $t_{1/2z}$, V_z, CL_{ss}, λ_z, $AUC_{\_\%Extrap}$, $MRT_{0\text{-}\infty,ss}$ and R_{ac} in MAD. The immunogenicity evaluation criteria will include the antidrug antibody positive rate before and after administration. The efficacy will be determined according to PASI 75, PASI 90, sPGA '0' or '1'; the ratio of PASI 75, PASI 90, sPGA '0' or '1' at different time points in the different administration arms will be compared (PASI 75/90: the proportion of patients whose PASI score was reduced by at least 75%/90% compared with the baseline level. sPGA '0' (clear) or '1' (minimum): the proportion of patients whose sPGA is 0 or 1 and have at least a two-point improvement).

The PASI score is calculated as follows：

PASI (head)=0.1 (erythema+infiltration+desquamation)×skin lesion area;

PASI (upper limb)=0.2 (erythema+infiltration+desquamation)×skin lesion area;

PASI (trunk)=0.3 (erythema+infiltration+desquamation)×skin lesion area;

PASI (lower limb)=0.4 (erythema+infiltration+desquamation)×skin lesion area;

PASI total score=PASI (head)+PASI (upper limb)+PASI (lower limb)+PASI (trunk).

Statistical analysis

The full analysis set will include all patients who were randomly allocated, and had received ≥1 dose of study drug with evaluation data. The safety set will include all patients who received ≥1 dose of study drug with safety evaluation data. The PK concentration set will include all patients who received study drug dose and had ≥1 quantifiable plasma concentration collected after dosing. The PK parameter set will include all patients who received the study drug dose and had ≥1 valid PK parameter collected after dosing. Continuous variables will be described as the means, SDs quartile, minimum and maximum. Dichotomous and categorical variables will be described as the frequency and percentage. Statistical analysis will be performed using SAS V.9.4. Significance will be set at a p value of 0.05.

Patient and public involvement

The patients and the public will not be involved in the design, conduct, reporting or dissemination plans of the research.

DISCUSSION

Psoriasis is a common inflammatory skin disease that is chronic and lifelong. Many patients remain untreated, do not respond to therapy or suffer from toxicities associated with traditional treatment, including phototherapy and systemic therapy. With the recent rapid development of biotechnology, the emergence of biological agents has led to safer and more effective treatment options for patients with psoriasis. The biological agents for the treatment of psoriasis include TNF-α inhibitors, IL-12/IL-23 inhibitors, IL-23 inhibitors and IL-17 inhibitors. Head-to-head studies have shown that the safety and anti-inflammatory efficacy of IL-17 inhibitors are superior to those of TNF-α inhibitors such as etanercept and adalimumab.[13–15] A systematic review and network meta-analysis including 28 studies showed that IL-17 inhibitors had superior efficacy to IL-12/IL-23 and IL-23 inhibitors.[16] Moreover, there is a negative correlation between patient body weight and response to treatment for many biologics such as TNF-α inhibitors and IL-12/IL-23 inhibitors, which means that overweight patients cannot achieve the same efficacy under the same dose as normal-weight patients.[17] However, IL-17 inhibitors do not present such problems, and all patients could obtain similar treatment outcomes regardless of their weight. Finally, IL-17 inhibitors have lower immunogenicity than other biologics, especially TNF inhibitors, indicating that its risk of causing unanticipated pharmacological effects and adverse drug reactions would be reduced.[18–20] GR1501 is a humanised IgG4 monoclonal antibody with high affinity for human IL-17 and high specificity to IL-17A (K_D=1.75 × 10^{-10} M). The similarity and differences between GR1501 and all approved IL-17 inhibitors are shown in the online supplemental appendix 3. GR1501 is expected to represent a therapeutic option for patients who are candidates for initial systemic therapy as well as those who have failed to respond or are intolerant to current therapies on the market.

The purpose of this study is to evaluate the safety, tolerability PK, immunogenicity and efficacy of GR1501 to guide the design of clinical trials in the next phases. Three biological agents for the management of psoriasis, secukinumab,[21 22] ixekizumab and brodalumab,[23 24] are already on the market. We compared our protocol with the protocols for these three drugs (online supplemental appendix 4) and observed that our study will accelerate the drug development process by seamlessly proceeding from the initial dose to a determined dose as is done in phase IIb trials.[25] Besides, considering the good safety profile of GR1501 from our preclinical data, to obtain PD/biomarker and surrogate data, to benefit patients as early as possible and to improve external validity, patients with related diseases will be included as subjects in our study; this could improve the generalisability of the trial results and speed up the drug development process. Moreover, in the expansion cohort, long-term (52 week) safety and efficacy assessments, which are not usually performed in phase I or phase II studies, will be performed.

We acknowledge the several limitations of our study. The maximum recommended starting dose (MRSD) in this study will be determined using the NOAEL method. NOAEL can be used to determine a relatively safe MRSD, but it may not take into account the pharmacological pathway of some important macromolecular agents. Owing to the differences between humans and animal species, especially in PD, affinity and efficacy, the prediction of MRSD for macromolecular drugs by the NOAEL method is often not accurate.[26] The European Medicines Agency recommended calculating a safe starting dose for macromolecular agents based on the minimal anticipated biological effect level.[27] Additionally, the selection of some categories of patients as subjects may bring potential risks. Concomitant diseases and medications may affect the accurate interpretation of safety data, leading to variability in the safety signals, a single or low dose may not provide sufficient therapeutic benefit to justify the inclusion of seriously ill patients in the study and the possibility of participating in subsequent trials may be ruled out.[27] Finally, the seamless design of the expansion cohorts might not provide accurate information to guide future trials but rather expose a large number of patients in multiple cohorts to potentially suboptimal or toxic doses.[25]

In conclusion, GR1501 is expected to represent an alternative therapy option for patients with plaque psoriasis, and this study will provide safety and possibly efficacy evidence for GR1501 through this phase I/II dose escalation and expansion trial.

ETHICS AND DISSEMINATION

The study will be practiced in compliance with this study protocol. The study is in accordance with the Declaration of Helsinki, and the ethics approvals of the protocol have been obtained from the ethics committees of all participating centres (including Peking University People's Hospital, Chinese PLA General Hospital, The First Affiliated Hospital, College of Medicine, Zhejiang University and The Second Xiangya Hospital of Central South University). Before the patients are enrolled in the trial, signed informed consent will be obtained (see online supplemental appendix 5). All changes and processes in the protocol will be approved by the ethics committees.

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Supplementary appendix 1. Selection criteria to participate in the study

Inclusion criteria	Those who meet all of the following conditions can be included.
1. Male or female patients aged 18-65 years. 2. Body mass index (BMI) 18-32 kg/m2 (not applicable in the case extension stage). 3. Diagnosed with chronic stable plaque psoriasis, baseline visit to psoriasis ≥ 6 months. 4. Psoriasis body surface area (BSA) ≥10% at screening and baseline. 5. Psoriasis static physician overall assessment (sPGA) score ≥ 3 and psoriasis area and severity index (PASI) score ≥ 12 at screening and baseline. 6. Moderate or severe plaque psoriasis patients who have been treated regularly but have poor results. 7. Patients who signed the informed consent.	
Exclusion criteria	Those who meet one of the following conditions will be excluded.
1. Pustular psoriasis, erythrodermic psoriasis and/or drip psoriasis at screening or baseline. 2. Drug-induced psoriasis at baseline. 3. Patients received the following treatments before baseline: a. Systemic treatment of psoriasis within 4 weeks prior to baseline; b. Local antipsoriatic medication within 2 weeks prior to baseline; c Any traditional Chinese medicine or Chinese patent medicine for psoriasis within 2 weeks before the baseline; d. Physical therapy treatment (including photochemotherapy, ultraviolet therapy, self-treatment with sunbed, etc.) within 4 weeks before the baseline. 4. The following biologics have recently been used: etanercept <28 days before baseline; infliximab, adalimumab or alefacept <60 days; golimumab <90 days; ustekinumab <8 months; rituximab; or all other biological agents <5 half-lives 5. Patients have received any biological agents that directly target IL-17 or IL-17 receptors. 6. Patients who have participated in other drug clinical trials within 3 months before the baseline, or those who have been tested within 5 half-lives before the baseline (the test drug has a long half-life and 5 half-lives of more than 3 months) 7. Vaccination with live vaccine within 4 weeks prior to baseline, or intention to inoculate a live vaccine during the study period. 8. Patients with active tuberculosis, or those with active or latent tuberculosis at the screening. 9. Patients who have a history of allergies to drugs or biological products, or those who are judged by the investigator to be allergic to any ingredient of the study drug. 10. Patients underwent major surgery within 8 weeks prior to the baseline or will be required to undergo such surgery during the study. Based on the investigator's opinion and consulting with the sponsor or its designee, these procedures may cause unacceptable risks to the patient. 11. History of the lymphoproliferative disease; or current history of malignancy or a history of malignancy (except for squamous cell carcinoma of the skin, basal cell carcinoma, and cervical cancer in situ after thorough treatment without any signs of recurrence). 12. Associated with an active infection, or infection history: a. Systemic anti-infective treatment 4 weeks before baseline; b. Serious infection with hospitalization or intravenous anti-infective treatment within 8 weeks before baseline; c. Recurrent, chronic or other active infections, which are assessed by the investigator to increase the risk of the subject. 13. Hepatitis B surface antigen positive, hepatitis C antibody positive, human immunodeficiency virus (HIV) antibody positive, TPPA positive (except for the addition of RPR	

negative).

14. ECG abnormalities that are clinically significant and can cause unacceptable risks to patients if they participate in the study.

15. Unstable cardiovascular disease, defined as clinical deterioration in the past 3 months (such as unstable angina, rapid atrial fibrillation) or hospitalization for heart disease in the past 3 months.

16. Hypertensive patients whose blood pressure cannot be stabilized after using hypertensive drugs.

17. Significant abnormalities in liver and kidney function and blood routine, including: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) exceeding 2 times the upper limit of normal; serum creatinine greater than the upper limit of normal; hemoglobin <90 g/L White blood cell count <3.5×109/L, platelet count (PLT)<100×109/L; neutrophil count <1.5×109/L; Other abnormal laboratory tests may affect the test or interfere with the test results assessed by the investigator.

18. Blood donation ≥ 400 mL within 4 weeks before baseline, or severe blood loss at least 400 mL within 4 weeks before baseline, or blood transfusion within 8 weeks, or blood donors scheduled for the study period.

19. Women of child-bearing potential are unwilling or not taking effective contraceptive measures from the screening period to at least 5 months after the end of the last dose.

20. Pregnant or nursing (lactating) women.

21. Patients who have a history of smoking, alcohol abuse or drug abuse.

22. Patients with a history of serious mental illness or family history.

23. Other reasons the investigator considered it inappropriate to participate in the study.

Supplementary appendix 2. Grade definition refers to the severity of the CTCAE Version 4.0.

Grade	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

CTCAE, common terminology criteria for adverse events; AE, adverse events; ADL, activities of daily living.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Supplementary appendix 3. The similarity and differences of GR1501 to any approved IL-17 inhibitors

Biological agents	Structure	Mechanism of action	Molecular weight	Affinity K_D
Secukinumab (AIN457)	Fully human IgG1κ anti-IL-17A monoclonal antibody	Selectively binds and neutralizes IL-17A	151kDa	1.75×10^{-10}M (for IL-17A)
Ixekizumab (LY2439821)	Humanized IgG4 anti-IL-17A monoclonal antibody	Selectively binds and neutralizes IL-17A	146kDa	<2 pM (for IL-17A)
Brodalumab (AMG 827)	Fully human IgG2 anti-IL-17RA monoclonal antibody	selectively targets human IL-17 receptor and antagonizes the IL-17 pathway.	144kDa	239 pM (for human IL-17RA)
GR1501	Fully human IgG4 anti-IL-17A monoclonal antibody	Selectively binds and neutralizes IL-17A	150kDa	1.39×10^{-10}M (for IL-17A)

Supplementary appendix 4. Comparison of protocol for biological agents targeting IL-17 in the treatment of psoriasis

Biological agents	Secukinumab (AIN457)		Ixekizumab (LY2439821)	Brodalumab (AMG 827)		GR1501
Phase	Phase I	Phase II	Phase II	Phase I	Phase II	Phase I/II
Sample size of participants	16		142	84	198	226
Allocation	Non-Randomized	Randomized	Randomized	Randomized	Randomized	Randomized
Masking	Open-label	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Triple (Participant, Care Provider, Investigator)	Triple (Participant, Investigator, Outcomes Assessor)	Double (Participant, Investigator)
Ages Eligible for Study:	18-65 Years	18 Years and older	18 Years and older	18-55 Years	18-70 Years	18-65 Years
Sexes Eligible for Study:	All	All	All	All	All	All
Accepts Healthy Volunteers:	Yes (healthy volunteers and psoriasis patients)	No	No	Yes (healthy volunteers and psoriasis patients)	No	No
Safety and tolerability measure	Yes	Yes	Yes	Yes	Yes	Yes
Pharmacokinetics measure	No	No	Yes	Yes	Yes	Yes
Immunogenicity measure	No	Yes	Yes	Yes	Yes	Yes
Efficacy measure	No	Yes	Yes	Yes	Yes	Yes
Treatment period	8-day	12-week	16-week	NA	12-week	Dose escalation: 12-week Expansion cohort: 52-week
Follow-up period	3-week	24-week	4-week	NA	4-week	Dose escalation: 10-week Expansion cohort: 4-week

Supplementary appendix 5. Patient consent forms

GR1501 注射液在斑块状银屑病患者中单次给药和多次重复给药的耐受性、药代动力学、免疫原性、剂量递增的安全性、初步疗效评价临床研究

知情同意书

研究方案编号 **：** GR1501-001

受试者筛选号 **：** □□□

受试者姓名缩写 **：** □□□□

研究负责人 **：**

研 究 单 位 **：**

申 办 单 位 **：** 重庆智翔金泰生物制药有限公司

智翔（上海）医药科技有限公司

知情同意书·知情告知页

尊敬的受试者：

我们真诚邀请您参加本研究。在您决定是否参加这项研究之前，请您尽可能的仔细阅读以下内容，可以帮助您了解该项研究，以及研究的具体内容、研究的流程和期限、参加研究后可能给您带来的益处、风险和不适。您是否参与本研究完全取决于您的意愿，无任何强迫。如果您拒绝参与本临床研究，您仍将继续接受治疗，并且不会影响您参与其他临床研究，您也可以选择其他治疗方案。当您有任何疑问时可以随时咨询我们，我们将给您详尽的解答。如果您愿意，也可以和您的亲属、朋友一起讨论，或者请研究医生给予解释。

本研究并已于 2018 年 04 月 11 日通过国家药品监督管理总局批准（批件号：2018L02322）。

【研究背景】

GR1501 注射液由智翔（上海）医药科技有限公司、重庆智翔金泰生物制药有限公司研制开发，其临床前研究表明在多种动物疾病模型中本品具有显著抑制模型动物的炎症严重程度作用，临床前药理、毒理学试验及国外同类型品种临床试验均揭示其安全性、耐受性良好。

【研究目的】

主要目的为评估斑块状银屑病患者单次和多次皮下注射给药后“GR1501 注射液”的安全性、耐受性。次要目的包括考察单次、多次皮下注射给药后“GR1501 注射液”在人体内的药代动力学参数，免疫原性和初步疗效。

【研究设计、研究内容、方法及程序简介】

本研究将严格遵守《药物临床试验质量管理规范》和《赫尔辛基宣言》。采用随机、双盲、安慰剂平行对照研究，在观察安全性、耐受性和初步疗效的同时，采集生物标本进行药代动力学及相关研究。本研究在北京大学人民医院、中国人民解放军总医院、浙江大学附属第一医院、中南大学湘雅二医院等中心开展。

本临床试验分先后两个阶段进行：剂量递增研究阶段（包括单次给药期、多次给药期、追踪随访期）和病例扩展研究阶段（多次给药期、长期给药期、追踪随访期）。

【参加研究的可能受益】

研究药物 GR1501 属于单克隆抗体药，如果您同意参加本研究，您的病情将有可能获得控制或缓解，但也可能不能控制或缓解。您参与并配合本研究，从中得到的信息在将来能够对和您病情相同的病人有指导意义。在此，为您对新药研发做出的贡献致以感谢。

【参加研究的可能风险】

GR1501 注射液的非临床安全性评价研究（包括组织交叉反应试验、小鼠安全药理试验、食蟹猴安全药理试验、食蟹猴急性毒性试验、食蟹猴长期毒性试验、免疫毒性试验、局部刺激性试验、体外溶血试验、过敏性试验等）结果显示本研究药品在动物试验中具有较好的安全性和耐受性。

【参加研究的不确定风险】

国外已上市的抗 IL-17 受体单抗 Siliq（Brodalumab）说明书中提示要特别关注自杀倾向和行为，但是与 GR1501 注射液相同靶点的已上市抗 IL-17A 单抗 Secukinumab 单抗和 Ixekizumab 单抗均未提示关于自杀倾向和行为的风险。为了更好控制受试者和试验的风险，在本临床研究“病例扩展研究阶段”中增加了哥伦比亚-自杀严重程度评定量表。

【有关内容的咨询】

您有权就有关研究内容进行咨询，咨询电话（研究者电话）：_____；且您有权就有关您的权利或相关风险等问题进行咨询，咨询电话（伦理委员会电话）：_____。

【退出研究】:

退出研究的权利：您参加此项研究是完全自愿的。如因任何原因，您不愿意参加或不愿继续参加此研究，并不会对您的权益有任何影响。此外，您有权在任何时间退出此研究，如果您不参加本项研究，或中途退出研究，还有很多可供您选择的其它替代的治疗药物和方法。如果您选择参加本项研究，我们希望您能够坚持完成全部研究过程。退出前所有从您那里收集的信息和研究样本，研究中心仍可利用，以便深入了解研究药物。如果您想退出本研究，请通知负责本研究的医师。他/她将安排您停止全部或部分的研究活动，并为您提供其他的护理。

【有关研究费用】

研究过程中，申办方免费提供试验期间内的试验药物以及研究相关的检查，比如血常规、血生化、心电图等检查。

【参加研究的补助】

合格入选并参与研究的受试者将得到适当的补助，补助的具体标准如下：①[redacted]；本研究阶段将进行 PK/ADA 采血：每个剂量组按方案规定完成全部给药计划的受试者需要采血 20 次。②[redacted]。本研究受试者完成全部随访，共约 21 次访视。补助将根据您的实际采血次数和来医院的访视次数，按银行卡转账和/或本人签收的形式分次进行。

因此，参加本阶段研究的受试者如果您按试验方案要求完成整个试验，[redacted]

GR1501 注射液治疗斑块状银屑病临床试验知情同意书

本研究的医护人员会以科学原则并尽最大责任把可能对您造成的伤害降到最低。您在整个研究期间采集的总血液量低于国家规定的献血时通常能够耐受的采血量。可能会采集额外的血液样品用于安全性评价。

【损伤补偿】

申办者除了对入组参加临床试验的您提供保险，并对于发生与试验相关的损害或死亡，承担治疗的费用及相应的经济补偿。

【可选的其他医疗方案】

您并非必须参与本研究才能获得针对您病情的治疗。如果您不参加本研究，您的研究医生可能根据您的病情安排其他替代治疗（如其他生物制剂、光疗等）。您可以与您的研究医生讨论这些替代治疗方案的风险与优点。

【保密制度】

您参加本临床研究以及在临床研究中的个人信息是严格保密的，您的医疗记录（包括原始病历、化验单等）将完整地保存在您所就诊的医院。您的病例报告表（CRF）等数据信息将以研究编号数字和您姓名拼音缩写而非您的姓名汉字加以标识，由研究者收集后提交申办方。可以识别您身份的信息将不会透露给研究小组以外的成员，除非获得您的许可。为确保研究过程符合法律、法规要求以及按照规定进行，研究者、申办方代表、伦理委员会成员、药品监督管理部门相关人员以及发生保险索赔时保险公司代表将被允许查阅您的医疗记录。关于本项研究的任何公开报告将不会披露您个人的任何身份信息。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私。

【怎样获得更多的信息】

研究期间，您可以在任何时间提出有关本项研究的任何问题。您的医生将给您留下他/她的电话号码以便能回答您的问题。

如果在研究过程中有任何重要的信息更新，可能会影响到您继续参加研究的意愿时，您的医生将及时通知您。

感谢您阅读以上信息。如果您决定参加本项研究，请告诉您的医生，他/她将会为您安排一切有关研究的事务。

如果在试验过程中出现预期以外的临床影响，我们将会对知情同意书的相关内容进行修改，并经受试者或其法定代理人重新签名确认。请您保留这份资料。

GR1501 注射液治疗斑块状银屑病临床试验知情同意书

知情同意书·同意签字页

本知情同意书一式两份，受试者和研究者各一份，双方签字后有效。

【受试者声明】

我已经阅读了上述有关本研究的介绍，而且有机会就此研究与医生讨论并提出问题，我提出的问题都得到了满意的答复。

我知道参加本研究可能产生的风险和获益。我明白：

我可以随时向医生咨询更多的信息。

我可以随时退出本研究，而不会受到歧视或报复，医疗待遇和其它权益不会受到影响。

我同样清楚，如果我中途退出研究，特别是药物的原因使我退出研究时，我若将病情变化告诉医生，完成相应的检查，这将对我本人和整个研究十分有利。

如果因病情变化我需要采取任何其它的药物治疗，我会事先征求医生的意见，或在事后如实告诉医生。

我同意药品监督管理部门、伦理委员会、监查员和稽查员查阅我的研究资料。

最后，我自愿参加本项研究，愿意与研究人员合作，本研究期间不参加其他临床研究。

受试者签名：_____ 身份证号码：_____

联系电话：_____ 日期：_____年____月____日

受试者法定代理人签名（必要时）：_____

联系电话：_____ 日期：_____年____月____日

独立第三方签名（必要时）：_____

联系电话：_____ 日期：_____年____月____日

【研究者声明】

我确认已向受试者解释了本试验的详细情况，包括其权利以及可能的受益和风险，并认真回答了受试者的所有有关问题；并将签署完成的知情同意书副本交给受试者保留。

研究者签名：_____

联系电话：_____ _____年____月____