Sirolimus for Antiphospholipid Antibody-Associated Thrombocytopenia: A National Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

Study Protocol

Item	Description
Protocol short name	SMART
Version	3.0
Version date	2026-06-09
NCT number	06722586
Project source	High-Quality Clinical Research Project of Peking University First Hospital
Sponsor	Department of Rheumatology and Immunology, Peking University First Hospital
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Planned study period	November 2024 to November 2027

Synopsis

Item	Description
Study title	Sirolimus for antiphospholipid antibody-associated thrombocytopenia: a national multicenter, randomized, double-blind, placebo-controlled, parallel-group study.
Condition	Antiphospholipid antibody-associated thrombocytopenia.
Study phase	Phase IV.
Study design	Randomized, double-blind, placebo-controlled, parallel-group phase for 6 months, followed by an optional 3-month open-label sirolimus extension phase for participants who do not achieve the primary endpoint at Month 6.
Sample size	84 participants randomized 1:1 to sirolimus or placebo; 42 participants per group.
Interventions	Double-blind phase: sirolimus 1 mg orally once daily versus matching placebo for 6 months. Optional open-label extension phase: sirolimus 1.5 mg orally once daily for 3 months.
Primary endpoint	Overall response rate at Month 6, defined as complete response plus partial response.
Secondary endpoints	Overall response rate at Month 1; overall response rate at Month 3; complete response rate at Month 6; partial response rate at Month 6; change from baseline in Global Antiphospholipid Syndrome Score (GAPSS) at Month 6; change from baseline in oral glucocorticoid dose at Month 6.
Other pre-specified outcomes	Percentage of open-label extension participants with overall response at Month 9; number of participants with serious adverse events during the double-blind treatment phase.
Study duration	The randomized double-blind phase lasts 6 months. Participants who meet criteria for the open-label extension phase may be followed through Month 9.
Study sites	Ten centers in China.

1. Background and Rationale

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombosis, recurrent obstetric morbidity, and persistent positivity for antiphospholipid antibodies (aPL). Thrombocytopenia is a common manifestation of APS, with reported prevalence ranging from 15% to 53%. Persistent thrombocytopenia has been associated with thrombotic events and poorer long-term prognosis in APS. Anticoagulation and antiplatelet therapy are important for thrombosis prevention, but persistent or severe thrombocytopenia and bleeding may limit antithrombotic treatment. Therefore, a safe and durable therapy for APS-related thrombocytopenia that may also reduce thrombotic risk is clinically needed.

Sirolimus, also known as rapamycin, is a macrolide compound with anti-fungal, anti-tumor, and immunosuppressive activity. It inhibits the mammalian target of rapamycin (mTOR) pathway and has immunomodulatory effects on both T cells and B cells. Activation of the mTOR pathway has been

investigated in systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and APS. In APS, mTOR pathway activation may contribute to thrombosis, obstetric morbidity, microvascular disease, and thrombocytopenia through effects on endothelial cells, platelets, monocytes, and other cellular pathways (Figure 1).

Clinical and translational evidence suggests a potential therapeutic role for sirolimus in APS and connective tissue disease-related thrombocytopenia. Sirolimus has been reported to reduce microvascular lesions and improve graft survival in kidney transplant recipients with APS nephropathy. Small single-arm studies in refractory connective tissue disease-related thrombocytopenia reported overall response rates of 60.0% and 66.7%. A single-center pilot study from the leading center reported that sirolimus monotherapy increased median platelet counts in primary APS-related thrombocytopenia and was associated with reductions in aPL titers. Common adverse reactions to sirolimus include hematologic, lipid, gastrointestinal, and skin abnormalities; most are mild to moderate and reversible after discontinuation.

No randomized controlled trial has evaluated sirolimus for aPL-associated thrombocytopenia. This national multicenter randomized trial is designed to objectively evaluate the efficacy and safety of sirolimus in this population and to provide evidence for clinical decision-making.

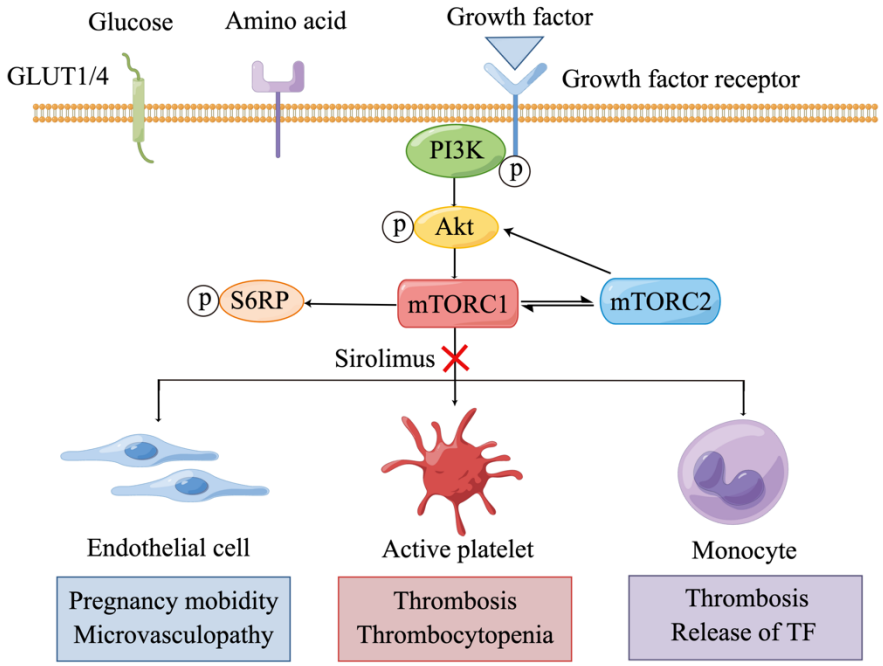


Figure 1. Ji L, Zhang Z, Perl A. Med Rev. 2023;0(0). doi:10.1515/mr-2023-0033

2. Objectives

2.1 Primary Objective

To evaluate the efficacy and safety of sirolimus for antiphospholipid antibody-associated thrombocytopenia.

2.2 Secondary Objectives

- To evaluate change from baseline in Global Antiphospholipid Syndrome Score (GAPSS) at Month 6.
- To preliminarily evaluate whether sirolimus facilitates oral glucocorticoid dose reduction.
- To describe the efficacy and safety of open-label extension treatment in participants who do not achieve the primary endpoint at Month 6.

3. Study Methods

3.1 Study Design

This is a national multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of sirolimus for antiphospholipid antibody-associated thrombocytopenia and evaluating prespecified secondary outcomes including GAPSS and oral glucocorticoid dose. Eighty-four participants will be randomized 1:1 to sirolimus or placebo, with 42 participants in each group. The randomized double-blind follow-up period lasts 6 months, and the primary endpoint will be assessed at Month 6. Participants who do not achieve the primary endpoint at Month 6, defined as overall response (complete response or partial response), may enter a 3-month open-label extension after investigator assessment of safety eligibility and renewed informed consent. Participants entering the extension will receive sirolimus 1.5 mg orally once daily.

After written informed consent and screening from Day -7 to Day 0, baseline data will be recorded. Follow-up visits will occur at Week 2 (Day 14 +/- 3 days), Month 1 (Day 30 +/- 7 days), Month 3 (Day 90 +/- 7 days), and Month 6 (Day 180 +/- 7 days). Participants entering the open-label extension will be followed through Month 9 (Day 270 +/- 7 days). At each visit, demographic information, medical history, vital signs, laboratory tests, disease assessment using GAPSS, adverse events, and serious adverse events will be recorded as applicable.

The study will prospectively collect clinical and biological information before and after sirolimus treatment in eligible outpatient and inpatient participants.

3.2 Randomization

Participants who provide informed consent, meet all inclusion criteria, and meet no exclusion criteria will be randomized in a 1:1 ratio to the sirolimus group or placebo group. Randomization numbers will be three-digit Arabic numerals from 001 to 084. If additional randomization lists are required because of erroneous randomization or sample size changes, additional numbers will start from 085 and will be generated using a new random seed with the same blinding format.

Randomization numbers will be assigned sequentially according to screening and enrollment order and will correspond to blinded drug numbers. An unblinded statistician independent of the study team will generate the randomization list using SAS version 9.4 or later, based on block randomization. The randomization list will include participant number, treatment assignment, and block. Emergency envelopes will be prepared according to the randomization list; each study drug package will correspond to one emergency envelope.

3.3 Study Drugs and Concomitant Therapy

During the double-blind phase, participants assigned to sirolimus will receive sirolimus 1 mg orally once daily, and participants assigned to placebo will receive an equal number of matching placebo tablets. Participants who do not achieve the primary endpoint at Month 6 and enter the open-label extension will receive sirolimus 1.5 mg orally once daily for 3 months. Conventional concomitant interventions may include hydroxychloroquine sulfate, aspirin, warfarin, rivaroxaban, dabigatran, and low-molecular-weight heparin.

Permitted concomitant medications

- Prednisone or equivalent glucocorticoid dose <=10 mg/day, stable for more than 2 weeks; intravenous and intramuscular glucocorticoids are not permitted.
- Hydroxychloroquine sulfate up to 5 mg/kg/day, with a maximum dose of 400 mg/day, stable for more than 3 months.
- Aspirin, warfarin, rivaroxaban, dabigatran, and low-molecular-weight heparin if used for more than 1 week and maintained at unchanged treatment intensity during the study period.

Prohibited medications

The following treatments are not permitted and should be discontinued for at least five half-lives before enrollment: thrombopoietin or thrombopoietin receptor agonists (including eltrombopag, hetrombopag, avatrombopag, and similar agents), immunoglobulin, immunosuppressive agents including azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, cyclophosphamide, leflunomide, and methotrexate, and B-cell-targeted therapies including belimumab, telitacicept, rituximab, obinutuzumab, and similar agents.

3.4 Blinding and Emergency Unblinding

The double-blind phase will blind participants, investigators, data managers, and statistical analysts. Blinding will be performed by designated personnel according to standard operating procedures for double-blind clinical trials. Matching placebo should be as similar as possible to sirolimus in dosage form, shape, color, external packaging, weight, solubility, taste, and odor, except for the active ingredient.

The sponsor will provide sirolimus and matching placebo. Study drug labels will include the protocol number, applicant, drug name or drug number, batch number, drug specification, package specification, dosage form, administration method, storage conditions, expiry date, and wording indicating use only for clinical trial purposes or equivalent wording. The complete drug coding process will be documented and quality checked.

The randomization list will be retained by the randomization unit. Emergency unblinding for an individual participant may occur only when knowledge of treatment assignment is necessary for management of an emergency. When feasible, the investigator should obtain approval from the site principal investigator before unblinding and should notify the sponsor within 24 hours after unblinding. The time, personnel, and reason for unblinding must be accurately documented, and treatment assignment information should be restricted to personnel with a need to know. Routine unblinding will not occur solely because a participant completes the Month 6 visit or enters the open-label extension.

Emergency unblinding may be considered, including but not limited to, serious adverse events suspected to be related to study drug or placebo and severe complications.

3.5 Study Population

Inclusion criteria

- Age >=18 years, regardless of sex.
- Persistent aPL positivity, defined as positivity for one or more of lupus anticoagulant (LA), anticardiolipin antibody (aCL IgG/IgM), or anti-beta2 glycoprotein I antibody (anti-beta2GPI IgG/IgM), with at least two positive results at least 12 weeks apart. Testing should follow relevant guidance from the International Society on Thrombosis and Haemostasis.
- LA will be tested using dilute Russell's viper venom time (dRVVT) and silica clotting time (SCT). Positivity by either method indicates LA positivity. Positivity by both dRVVT and SCT is defined as double-method LA positivity. For participants receiving warfarin, LA results will be recorded only when the international normalized ratio is <1.5.
- aCL (IgG/IgM) and anti-beta2GPI (IgG/IgM) will be tested using enzyme-linked immunosorbent assay (ELISA) and reported in RU/mL. Titers above the 99th percentile are considered positive, corresponding to 12 RU/mL for aCL and 20 RU/mL for anti-beta2GPI. Titers >40 RU/mL are defined as medium-to-high titer positivity.
- Persistent platelet count reduction, defined as platelet count between 30 and 100 x 10^9/L, with a normal reference range of 125 to 350 x 10^9/L, persisting for at least 2 weeks.
- Voluntary participation and signed informed consent.

Exclusion criteria

- Meeting classification criteria for connective tissue diseases other than APS, including but not limited to systemic lupus erythematosus and Sjögren syndrome.
- Receipt of oral or intravenous antibiotics within 2 weeks before enrollment.
- Acute thrombosis, defined as new thrombosis within 4 weeks.
- Marked bleeding tendency or existing severe bleeding manifestations, including cerebral hemorrhage, gastrointestinal bleeding, genitourinary bleeding, or oral mucosal bleeding.
- Life-threatening and/or organ-threatening manifestations, including but not limited to catastrophic APS and thrombotic microangiopathy.
- Hepatic or renal dysfunction: ALT and/or AST >3 times the upper limit of normal, or estimated glomerular filtration rate <40 mL/min/1.73 m2.
- Cytopenia: white blood cell count <3 x 10^9/L or hemoglobin <100 g/L.
- Uncontrolled lipid metabolism disorder: low-density lipoprotein cholesterol >3.1 mmol/L or triglycerides >2.3 mmol/L after lipid-lowering therapy.
- Active infection, including but not limited to bacterial, viral, tuberculosis, or fungal infection.
- Pregnancy or puerperium within 6 weeks after delivery; women of childbearing potential are required to use contraception other than oral contraceptives. Lactating women are excluded.
- Known intolerance to the study drug.
- Current participation in another interventional drug clinical study.

Withdrawal criteria

- Platelet count <20 x 10^9/L at any follow-up stage in either group.
- Serious bleeding event at any follow-up stage in either group.
- Participant request to withdraw at any stage of the study.

Open-label extension entry criteria

Not achieving the primary endpoint at Month 6 is defined as failure to achieve overall response, namely failure to achieve complete response or partial response, after 6 months of study treatment. Failure to achieve the primary endpoint at Month 6 is not a mandatory withdrawal criterion. After completing Month 6 efficacy and safety assessments, participants may enter the open-label extension based on investigator judgment and renewed informed consent. Participants entering the extension will stop the original blinded study drug and receive open-label sirolimus 1.5 mg orally once daily for 3 months.

Participants will be recruited consecutively from outpatient and inpatient settings at participating centers if they meet inclusion criteria and no exclusion criteria. No matching is required because randomization is used to balance the two groups.

3.6 Follow-up Schedule

At baseline, participants will be randomized 1:1 to sirolimus or placebo. The sirolimus group will receive sirolimus 1 mg once daily, and the placebo group will receive an equal number of matching tablets. Double-blind follow-up will occur at Week 2, Month 1, Month 3, and Month 6. Complete response, partial response, and overall response will be assessed at Months 1, 3, and 6. The primary endpoint will be assessed at Month 6. Participants who do not achieve the primary endpoint at Month 6 and enter the open-label extension will receive 3 months of open-label sirolimus 1.5 mg once daily and will be followed through Month 9. Blood samples will be collected at Months 1, 3, and 6 and transported under cold-chain conditions to the central laboratory of the leading site for sirolimus trough concentration testing.

An independent medical monitor may reduce the sirolimus dose according to efficacy and sirolimus trough concentration. If the sirolimus trough concentration is >15 ng/mL, the sirolimus dose may be reduced to 0.5 mg once daily, and participants in the placebo group will receive the corresponding blinded reduction to 0.5 mg once daily to preserve blinding (Figure 2).

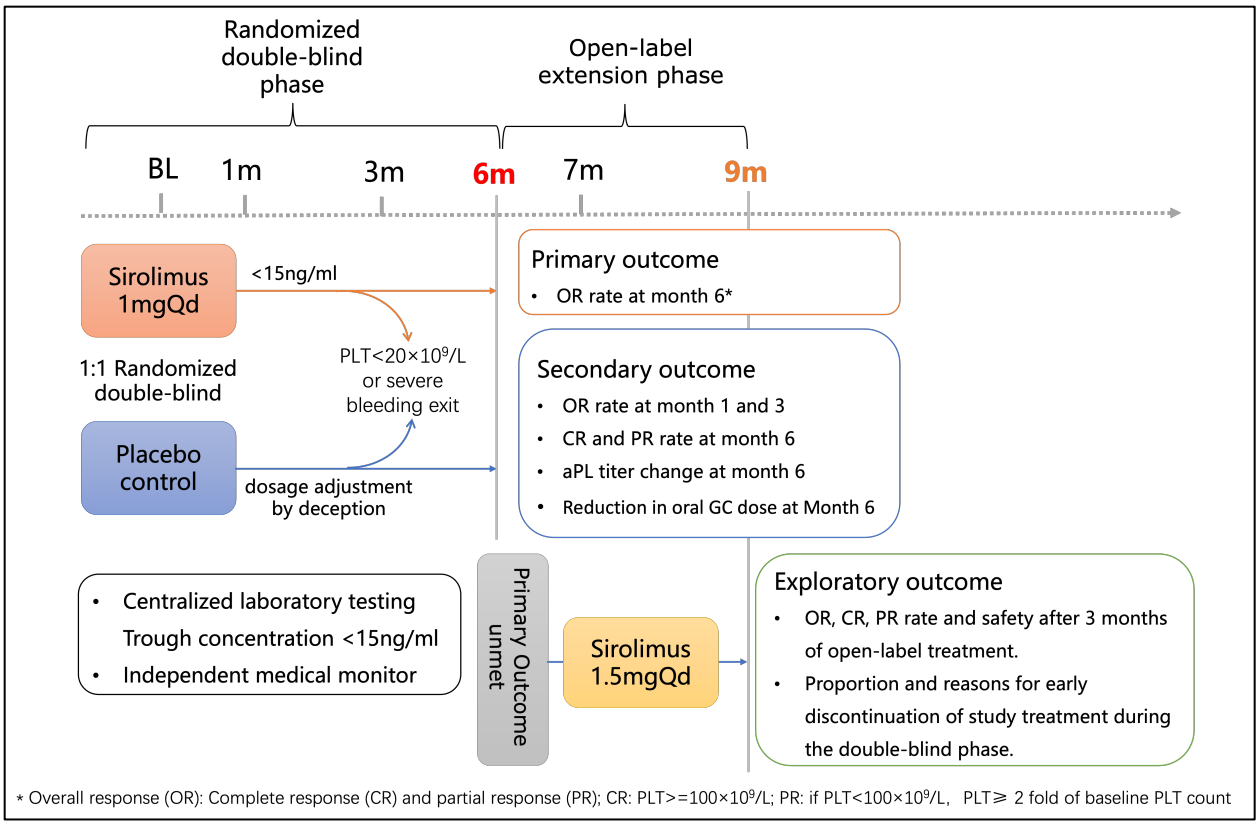


Figure 2. Clinical study flow and protocol procedures.

Table 1. Follow-up schedule.

Assessment	**Screening/Baseline D-7 to D0**	**Week 2 +/-3 d**	**Month 1 +/-7 d**	**Month 3 +/-7 d**	**Month 6 +/-7 d**	**Month 7 +/-7 d**	**Month 9 +/-7 d**
Informed consent, demographics, history, inclusion/exclusion criteria	Y						
Vital signs and physical examination	Y	Y	Y	Y	Y	Y	Y
Complete blood count	Y	Y	Y	Y	Y	Y	Y
Liver/renal function, electrolytes, lipids	Y		Y	Y	Y	Y	Y
Urinalysis	Y		Y	Y	Y	Y	Y
Urine hCG for women	Y						
UPCR/UTP	Y		Y	Y	Y	Y	Y
Sirolimus trough concentration		Y	Y	Y	Y	Y	Y
ANA profile	Y						

LA by dRVVT and SCT	Y			Y	Y		Y
aCL IgG/IgM	Y			Y	Y		Y
Anti-beta2GPI IgG/IgM	Y			Y	Y		Y
Anti-PS/PT IgG/IgM	Y			Y	Y		Y
Immunoglobulins and complement	Y						
Basic research blood samples	Y		Y	Y	Y	Y	Y
Echocardiography	Y						
GAPSS disease assessment	Y			Y	Y		Y
Adverse events/serious adverse events		Y	Y	Y	Y	Y	Y

Note: Participants not achieving the primary endpoint at Month 6 may enter the open-label extension after completing Month 6 efficacy and safety assessments. Extension treatment is sirolimus 1.5 mg once daily for 3 months, with follow-up through Month 9.

3.7 Efficacy and Safety Endpoints

Primary efficacy endpoint

Overall response rate at Month 6 after study treatment among participants with thrombocytopenia, defined as complete response plus partial response.

Complete response is defined as platelet count >=100 x 10^9/L.

Partial response is defined as platelet count <100 x 10^9/L with at least a 2-fold increase from baseline.

Participants with missing Month 6 assessment or meeting prespecified treatment failure criteria will be counted as non-responders.

Secondary efficacy endpoints

- Overall response rate at Month 1;
- Overall response rate at Month 3;
- Complete response rate at Month 6;
- Partial response rate at Month 6;
- Change from baseline in Global Antiphospholipid Syndrome Score (GAPSS) at Month 6;
- Change from baseline in oral glucocorticoid dose at Month 6.

Other pre-specified outcome measures

- Percentage of open-label extension participants with overall response at Month 9;
- Number of participants with serious adverse events during the double-blind treatment phase.

Safety monitoring

Safety monitoring will include adverse events, serious adverse events, vital signs, and physical examination findings from initiation of study drug through study completion.

3.8 Adverse Event Definitions, Assessment, and Reporting

An adverse event (AE) is any unfavorable medical event after administration of study drug, whether or not causally related to the study drug. AEs may include symptoms, signs, diseases, or abnormal laboratory findings. AEs include treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs).

A TEAE is an event that occurs during or after administration of study drug and was not present before treatment or is worse than before treatment.

An SAE is an adverse medical event after administration of study drug that results in death, is life-threatening, causes permanent or severe disability or dysfunction, requires hospitalization or prolongs hospitalization, or results in congenital anomaly or birth defect.

An ADR is any harmful or unintended response in a clinical trial that is possibly related to the study drug. A reasonable possibility of causality means that a relationship cannot be excluded.

A SUSAR is a suspected and unexpected serious adverse reaction whose nature and severity exceed available information such as the investigator's brochure, approved label, or product characteristics.

Physical examination includes height, weight, and gynecologic examination as applicable. Vital signs include systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature measured with the participant seated and at rest at each visit.

Table 2. Severity grading for adverse events.

Severity	Description
Mild	Discomfort is present but does not affect normal daily activities and does not require medical intervention.
Moderate	Discomfort is sufficient to reduce or affect normal daily activities and may require medical intervention.
Severe	The participant is unable to work or has severe effects on normal daily activities, including functional impairment, requiring medical intervention.

Investigators will assess the relationship between each AE and study treatment. Evidence supporting a related assessment may include consistency with the known pharmacology of the drug, known class effects, reasonable temporal relationship to exposure, recurrence on rechallenge, absence of a more plausible alternative cause, rarity in unexposed populations, and a dose-response relationship. Evidence supporting an unrelated assessment may include an implausible temporal relationship, persistence after discontinuation considering drug pharmacology, more plausible alternative explanations, or resolution despite continued treatment.

AE outcomes may be recorded as recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, or unknown. All AEs and SAEs must be followed until a final

outcome is determined, including after study completion if needed, until the event is resolved, stabilized, reasonably explained, the participant is lost to follow-up, or death occurs.

AE collection begins when the participant starts study drug and continues until study completion. Sources include spontaneous participant reports, investigator questioning, and clinically significant changes or abnormal findings identified by the investigator. All AEs, regardless of causality, must be recorded in source documents with at least the AE term, start date, severity, causal relationship, actions taken, outcome, and end date if applicable. AE terms should preferably use a medical diagnosis; if no diagnosis is available, symptoms or signs may be recorded and updated once a diagnosis is established.

All deaths during the study period must be reported immediately to the sponsor. Investigators should provide necessary materials to the sponsor and ethics committee, including autopsy reports and final medical reports when available. All SAEs, whether or not related to the study drug, must receive timely medical management and be reported in writing to the sponsor immediately, followed by detailed written follow-up reports. The sponsor should continue tracking serious adverse reactions after the initial report and submit new information or amendments to previous reports within 15 days of obtaining new information.

3.9 Sample Size

This randomized controlled trial compares sirolimus with placebo, with platelet response rate as the primary evaluation indicator. Based on preliminary exploratory data, the 6-month overall response rate in the sirolimus group was 85.7%. Assuming an expanded-sample response rate of 60% in the sirolimus group and 30% in the placebo group, with two-sided alpha of 0.05, power of 80%, and a 1:1 allocation ratio, a superiority hypothesis test requires 38 participants per group. Allowing for 10% loss to follow-up or refusal of follow-up, at least 42 participants per group, for a total of 84 participants, are required. The leading center plans to enroll 30 participants.

3.10 Data Management and Statistical Analysis

Investigators will retain timely, complete, accurate, and clear data based on original observation records and archive them by participant number.

Analysis sets

- Full analysis set (FAS): all randomized participants, analyzed according to their randomized treatment assignment. Participants will not be excluded because of nonadherence, treatment discontinuation, protocol deviations, or missing outcome data, except for rare prespecified circumstances such as erroneous randomization with no study intervention administered.
- Per-protocol set (PPS): participants who complete primary efficacy endpoint assessment and have no major protocol deviations affecting primary efficacy evaluation, such as violation of eligibility criteria or poor compliance.
- Safety analysis set (SS): all participants who receive at least one dose of study drug, analyzed according to actual treatment received.

Data will be analyzed using R statistical software. All statistical tests will be two-sided, with the overall type I error controlled as specified for the primary endpoint and multiplicity-adjusted secondary endpoint analyses. Continuous variables will be summarized as mean +/- standard deviation if normally

distributed, or median and interquartile range otherwise. Categorical variables will be summarized as frequency and percentage. For continuous variables, between-group comparisons will use t tests when normality and homogeneity of variance are met; analysis of variance will be used for multi-group comparisons. If normality is not met, Wilcoxon rank-sum tests or Kruskal-Wallis tests will be used as appropriate. Categorical variables will be compared using chi-square tests or Fisher exact tests according to applicable conditions. Confidence intervals will use 95% confidence levels unless otherwise specified in the alpha-spending plan.

Primary efficacy analysis

The primary efficacy analysis will be performed in the FAS. For the primary endpoint, the number and percentage of participants with overall response at Month 6 will be summarized by randomized group. The primary effect measure will be the between-group risk difference in overall response rate, calculated as the sirolimus group minus the placebo group, with a 95% confidence interval estimated using the Newcombe score method without continuity correction or another prespecified exact/score-based method if sparse data require it. Superiority of sirolimus over placebo will be concluded if the two-sided hypothesis test for the primary endpoint is statistically significant at the alpha level determined by the prespecified alpha-spending plan and the point estimate favors sirolimus. Risk ratio and odds ratio with 95% confidence intervals will be reported as supplementary effect measures. Participants with missing Month 6 primary endpoint assessment, early discontinuation because of poor efficacy, platelet count <20 x 10^9/L, serious bleeding, use of prohibited rescue therapy, withdrawal of informed consent without evaluable Month 6 efficacy data, or loss to follow-up before the Month 6 assessment will be classified as non-responders in the primary analysis. Sensitivity analyses will include complete-case analysis, multiple imputation under a missing-at-random assumption when data support it, and best-case/worst-case or tipping-point analyses to evaluate robustness to missing outcome assumptions. Multivariable logistic regression will be used as a sensitivity analysis to adjust for clinically relevant baseline prognostic factors, including age, sex, baseline platelet count, baseline glucocorticoid use, and study center or pooled center/region where feasible, with adjusted odds ratios and 95% confidence intervals reported.

Secondary efficacy analysis

Secondary efficacy endpoints will be analyzed after the primary endpoint. Multiplicity across the prespecified secondary endpoint family will be controlled using the Holm-Bonferroni procedure at the two-sided family-wise alpha level of 0.05, or at the remaining alpha level specified by the alpha-spending plan if applicable. Both nominal and multiplicity-adjusted P values will be reported. Exploratory endpoints will not be included in this multiplicity adjustment.

- For overall response at Month 1 and Month 3, analyses will be conducted separately. The number and percentage of participants with CR+PR will be summarized at each time point. Overall response rates and 95% confidence intervals for each group, and rate differences with 95% confidence intervals, will be calculated using score-based or exact methods as appropriate. Between-group differences will be tested using chi-square or Fisher exact tests as appropriate.
- For complete response at Month 6, the number and percentage of participants with CR will be summarized. Group-specific CR rates and 95% confidence intervals, and between-group differences

with 95% confidence intervals, will be calculated using score-based or exact methods as appropriate. Between-group differences will be tested using chi-square or Fisher exact tests.

- Partial response at Month 6 will be analyzed using the same method as complete response.
- Change from baseline in GAPSS at Month 6 will be summarized as Month 6 GAPSS minus baseline GAPSS. GAPSS will be calculated according to the prespecified scoring algorithm based on antiphospholipid antibody profile and cardiovascular risk factors.
- Change from baseline in oral glucocorticoid dose at Month 6 will be summarized after conversion to prednisone-equivalent dose.

Other pre-specified outcome analyses

Other pre-specified outcomes will be analyzed descriptively. Participants who do not achieve the Month 6 primary endpoint will be included in the Month 6 primary efficacy analysis according to original randomized assignment and classified as non-responders for overall response. The open-label extension will not alter the Month 6 primary endpoint analysis, the randomized treatment assignment, or the interpretation of the double-blind phase. Among participants who enter the open-label extension, overall response at Month 9 will be summarized as the number and percentage of extension participants achieving complete response or partial response. No confirmatory comparison with double-blind efficacy outcomes will be performed. Serious adverse events occurring from first dose through Month 6 during the double-blind treatment phase will be summarized as the number of participants with serious adverse events by randomized group.

Safety analysis

Safety analyses will be conducted in the safety analysis set. The number of participants and events for AEs and treatment-related AEs will be described, and incidence will be calculated. Between-group comparisons will use chi-square or exact tests. Vital signs at each visit and changes from baseline, including systolic and diastolic blood pressure, body temperature, heart rate, and respiratory rate, will be described. Between-group comparisons will use independent-sample t tests, and within-group comparisons will use paired t tests. Physical examination findings will be described using categorical summaries and compared between groups using chi-square or Fisher exact tests.

Interim analysis

An interim analysis is planned when 58 participants have completed 6 months of follow-up. The overall two-sided type I error rate for the primary endpoint will be controlled at 0.05 using a prespecified alpha-spending method, such as a Lan-DeMets alpha-spending function approximating an O'Brien-Fleming boundary. The exact interim and final efficacy boundaries, information fraction, and decision rules will be specified in the statistical analysis plan before database access for the interim analysis. The interim analysis will be reviewed by an independent data monitoring committee while maintaining the blind for the study investigators, participants, site staff, data managers, and other members of the blinded study team. Early termination for overwhelming efficacy may be considered only if the prespecified interim efficacy boundary is crossed and after review by the independent data monitoring committee and approval by the ethics committee.

4. Participant Protection

Participants have the right to voluntarily choose whether to participate in this study. Participation does not require additional payment. The study provides compensation of 200 RMB per visit for transportation and lost work time, with no additional remuneration. If a participant's health is harmed because of participation in this study, investigators will promptly take necessary medical measures and provide compensation according to applicable national laws.

5. Quality Control

The clinical study will begin after ethics committee approval. Any major modification during implementation must be submitted to and approved by the ethics committee before implementation. Non-substantive modifications will be discussed and decided by investigators and statisticians, and the latest version will be submitted to the ethics committee for filing.

Personnel at all participating centers will receive unified training and will use unified recording methods and evaluation criteria. Abnormal laboratory tests will be judged according to the normal reference ranges of each center. To ensure data reliability, all observations and findings in the clinical study will be verified so that study conclusions derive from source data. Appropriate data management measures will be used during clinical study conduct and data processing.

Study termination criteria and procedures

If unexpected, major, or unacceptable risks to enrolled participants are identified during the study, or if data quality and compliance cannot meet Good Clinical Practice requirements, the study may be stopped early to protect participants and ensure study quality. When early termination is proposed, written reasons will be provided and the ethics committee will be notified. All enrolled participants will continue follow-up according to the protocol until study exit.

Record retention

Original records, including all participant information and related source documents such as signed informed consent forms and relevant records, will be properly retained. According to Good Clinical Practice requirements, all clinical study documents will be retained for at least 5 years after study completion.

6. Study Timeline

- Year 1 (November 2024 to November 2025): enroll 50% of the planned sample size.
- Year 2 (November 2025 to November 2026): complete enrollment and follow-up for 50% of participants and conduct the interim analysis.
- Year 3 (November 2026 to November 2027): complete enrollment and follow-up for all participants, analyze results, and prepare manuscripts.

7. Publication of Study Results

Study results may be published as manuscripts, conference abstracts, patents, or other forms. Participant-identifiable personal information will not be disclosed when study results are published without participant permission.

8. Funding

National High Level Hospital Clinical Research Funding, High Quality Clinical Research Project of Peking University First Hospital 2024HQ06.