A Phase III Clinical Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with Systemic Lupus Erythematosus: Main Activities during the Start-Up Period

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Abstract

**Introduction.** The start up of a trial is a critical period for the clinical trial quality, budget and timelines. Any decision taken during this period will impact these three elements.

**Background.** Atacicept is a protein which acts as an antagonist to B-lymphocyte stimulator and a proliferation-inducing ligand that are both increased in subjects with Systemic Lupus Erythematosus (SLE). SLE is a chronic autoimmune disease characterized by a variety of clinical manifestations.

**Hypothesis.** The pre clinical and clinical documentation supports the administration of atacicept in subjects with SLE according to the proposed clinical trial protocol.

**Objective.** The purpose of this trial is to evaluate the efficacy and safety of atacicept compared to placebo in subjects with SLE. This trial will be part of a registration package. Atacicept is planned to be on the market by 2015.

**Methods.** During the study start-up, major decisions have been made and implemented, such as outsourcing, feasibility, submission strategy and protocol finalization.

**Results.** No clinical trial results are available yet. However, some of the activities I was involved in are described in this report.

**Discussion and conclusion.** Some strategic decisions have been made and a lot of challenges were raised for the atacicept program. These decisions will have an impact on the study deliverables.
Introduction

Merck Serono is actively committed to bringing therapeutic innovations to patients, and is specialized in treatments for diseases with unmet medical needs, such as cancers, neurodegenerative diseases, infertility, endocrine and metabolic disorders, cardiovascular diseases and other life-altering conditions for which there is currently no cure. Merck Serono’s R&D pipeline currently includes 30 projects in clinical development [1].

The Global Clinical Operations (GCO) department oversees all the aspects of clinical project management, including clinical trial leadership and coordination, biostatistics, clinical monitoring, data management or medical writing. Within the GCO, the Clinical Trial Management (CTM) Full Development department manages the coordination of phase II, III and IV trials, in collaboration with other departments (Clinical Trial Supplies, Quality Assurance, Data Management, Safety, Regulatory, Statistics, Medical department, Clinical Monitoring, Medical Writing and Human Pharmacology). The main objective of the CTM department is to lead the cross-functional trial teams, in order to deliver the study within timelines and budget, and ensure the quality of the clinical trial.

During the start-up of a study, main activities of CTM representatives consist in leading and coordinating the different tasks, ensuring that the vendor(s) (if any) is properly conducting the delegated tasks, delivering the study specific documents and evaluating the specific needs for the conduct of the trial.

From February 2010, I have been actively involved in the start-up of two global phase III studies, named Alpine I and Alpine II, of atacicept in subjects with Systemic Lupus Erythematosus (SLE). I was an active member of the trial teams, supporting the Clinical Trial Leaders (CTL). This role within the trial teams gave me the opportunity to work closely with different functions involved in the clinical trial management, to learn how to properly conduct the start-up a phase III global program in a highly competitive landscape and to deal with some strategic decisions from the company.

This internship report will be focused on Alpine I, as well as on my main activities within the trial team. However, to better define some of these activities, it will be necessary to mention Alpine II as well. The first part is dedicated to atacicept and SLE. In a second part, I will describe the objectives of the clinical trial and the methods used to reach them. Finally, I will discuss the expected results and the methodology used for this study.

Background information

1. Atacicept

Atacicept is a recombinant fusion protein composed of two parts (Appendix 1), which acts as an antagonist to B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), both members of the tumor necrosis factor (TNF) superfamily. The current literature suggests a crucial role for BLyS, APRIL, and their receptors in B cell development, survival, and maintenance [2,3,4]. The ability of atacicept to block the effects of BLyS and APRIL, and the resultant inhibition of autoantibody production, suggest that atacicept may limit the extent of tissue damage observed in subjects with autoimmune disease. This is supported by the increased levels of both BLyS and APRIL that have been measured in serum samples from SLE subjects and in the synovial fluid of subjects with Rheumatoid Arthritis (RA) [2,5,6]. There is a strong rationale for treating subjects with SLE using an inhibitor of BLyS and APRIL. Belimumab, an agent developed by Human Genome Science and Glaxo SmithKline, which inhibits BLyS only, has recently shown efficacy and safety in this indication [7].
Atacicept is currently under investigation in phase II clinical trials in RA and in a phase II/III study in SLE. Data from these studies show atacicept is well tolerated. In addition to these ongoing studies, 2 phase III studies are planned to start in SLE. These two new studies will evaluate efficacy as a primary endpoint. In addition to these pivotal studies, a phase Ib study of atacicept in Lupus Nephritis is currently in the start-up phase, and will be launched before the end of 2010.

2. Systemic Lupus Erythematosus

SLE is a chronic, potentially fatal, autoimmune disease characterized by unpredictable exacerbations and remissions, a variety of clinical manifestations such as fatigue, arthritis, rashes, nephritis and multiple autoantibodies. Prevalence varies with ethnicity, being higher in African American and other non-Caucasian populations, but is estimated to be about 1 per 1000 overall [8,9,10]. SLE is up to 9 times more common in women than men, and typically has a predilection for women in their child-bearing years [8]. Subjects with moderate to severe SLE consider their quality of life to be poor, and they are chronically exposed to drugs associated with significant side effects, such as corticosteroids and general immunosuppressive agents.

The disease manifestations in SLE result from recurrent injury due to immune complex deposition, leukothrombosis, or thrombosis. Additionally, cytotoxic antibodies can mediate autoimmune hemolytic anemia and thrombocytopenia, while antibodies to specific cellular antigens can disrupt cellular function. Treatment with atacicept is expected to reduce B cell numbers and consequently the level of autoantibodies, thereby ameliorating progression of the disease.

Hypothesis

The available toxicological and clinical documentation supports the administration of atacicept in subjects with SLE according to the proposed clinical trial protocol. Given the current stage of development of atacicept, it is unknown whether subjects in this trial can expect any clinical benefit from receiving atacicept. However, given the current safety data and the controls in place to minimize the risk from infections, the risk-benefit balance in this phase III trial is considered positive (or favorable). It is also supported by the validation of this pathway as a promising target for SLE therapy by the two phase III trials of belimumab, a drug developed by one of our competitors.

Objectives

The purpose of Alpine I is to evaluate the efficacy and safety of atacicept compared to placebo in subjects with SLE treated with standard of care (SoC) therapy. Alpine I is a multicenter, randomized, double-blind placebo-controlled (DBPC), parallel-arm trial.

Alpine I and II are based on the same design and with the same objectives, but with different secondary endpoints, and are conducted in different countries. These two studies will also evaluate pharmacodynamic responses to better understand the effects of atacicept in this disease. They will complement the currently ongoing phase II/III study, which evaluates the efficacy of atacicept in maintaining low disease activity in subjects with SLE, and will be included in the submission dossiers for marketing authorization. Atacicept is planned to be launched on the market by 2016.

Methods

1. Trial methodology
Alpine I is a trial composed of a 3-week screening period, a 52-week DBPC treatment period, and a 24-week follow-up period. The total duration of each subject’s participation in the trial will be up to 79 weeks. The design is described in appendix 2.

The primary endpoint is a landmark analysis, based on three specific tools for the assessment of SLE activity: the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) score, the Physician’s Global Assessment (PGA), and the British Isles Lupus Assessment Group (BILAG) 2004 score. Efficacy will also be evaluated through assessment of the individual components of the primary endpoint composite responder index, as well as the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) damage index. Steroid usage will also be captured and assessed as a major secondary endpoint.

Major efficacy secondary endpoints will be tested sequentially in the order of the following bullet points below:

- Mean change in Medical Outcomes Study Short-Form General (SF-36) Health Survey physical component summary score (PCS) at Week 52.
- Proportion of subjects whose prednisone dose has been reduced from Study Day 1 by ≥ 25% to 7.5 mg/day during Weeks 36 through 52.

Safety assessments will include monitoring of Adverse Events (AE), local tolerability, laboratory parameters, vital signs, ECG, and physical examination. Subjects will be asked to record, in a subject diary, details of trial medication administration/intake, AEs, injection site reactions, and any changes in concomitant medications and procedures. An Independent Data Monitoring Committee (IDMC) will periodically review interim safety and efficacy data and make recommendations to the Sponsor’s Global Safety and Ethics Committee (GSEC) for the safe conduct of the trial. Particular attention will be paid to SLE disease activity, as well as events consistent with infectious or potentially demyelinating disease.

2. Strategic methods

2.1. Outsourcing

The company strategy is to conduct the study under a new model of outsourcing: the study is fully outsourced to a Contract Research Organization (CRO), from the protocol concept sheet to the clinical trial report. Nevertheless it has been decided that some critical activities such as drug safety reporting, statistical analysis of the data and clinical trial report writing should remain under direct company’s responsibility. This split of activities between the Sponsor and the CRO are described in the Project Addendum (contract). The CRO has to deliver on a regular basis a study status update report including different milestones, and the Merck Serono trial team had to put in place some surveillance of the CRO activities.

2.2. Feasibility and competitive landscape

The feasibility has been conducted in 64 countries, for the two ALPINE studies, from January to June 2010. It is planned to randomize more than 900 subjects in each trial. Each trial is planned to be performed in approximately 200 centers in regions including (but not restricted to) Western and Eastern Europe, North America, Latin America and Asia-Pacific. The company provided the CRO with nominations of recommended sites, which were good recruiters in previous SLE studies or with special interest for atasicept.

The competitive landscape in the SLE field was also a huge challenge in this feasibility and investigators recruitment processes. Indeed, three competitors were planning to launch their phase III or per-approval studies at the same time. Therefore the feasibility was performed in a highly competitive landscape. The company also faced internal competition since the phase
II/III study of atacicept in SLE was still ongoing at the time of the feasibility. The assumption for the overall SLE program (Alpine I and II and three competitors) is that more than 12000 patients need to be included.

In order to move beyond this huge challenge, some specific trial recruitment strategies have been put in place by the trial teams:
- contact with Lupus professional associations to use their contact network, and presence of Merck Serono at Lupus congresses
- a web link has been sent to potential investigators for completing an online survey
- a contact with Lupus patients associations will be made and a study-specific website will be created to advertise about the study
- a study-specific branding has been created to differentiate from other clinical trials

2.3. Alpine I: study protocol

Based on the final concept sheet, the protocol was written by the CRO under Merck Serono medical guidance and surveillance, using the Merck Serono template. The first draft was available at the end of January 2010, and the final draft was expected at the end of April 2010, in order to be submitted to the FDA. During these 4 months of review, the protocol has been reviewed by Merck Serono’s and CRO’s trial teams, by the 2 worldwide coordinating investigators and by Lupus experts. An audit has also been conducted on the second draft of the protocol by the Merck Serono Development Quality Assurance (DQA) department.

Regarding the submission of the protocol to Health Authorities (HA) and Ethics Committees (EC), it has been decided to wait for the initial FDA consultation feedback on the final draft of the protocol before before submitting it to HAs or ECs in any country.

2.4. Informed Consent Form (ICF)

I was delegated the task of drafting the master ICF in collaboration with the CRO medical writer. This document was drafted by the CRO, and underwent 3 cycles of review within the trial team. These three review cycles involved several departments such as Global Drug Safety, Legal, Regulatory Affairs, Exploratory Medicine and Clinical Monitoring. I was in charge of coordinating the review with internal trial team members, as well as ensuring the document was drafted and approved according to agreed timelines by both parties.

As the study is planned to be conducted in the US, the Health Insurance Portability and Accountability Act (HIPAA) form is required, therefore had to be drafted and approved by Merck Serono, in addition to the ICF. I have also been delegated the coordination of the HIPAA form review.

2.5. Communication plan

For such an international study fully outsourced to a CRO, we had to set-up a communication plan for both Merck-Serono and CRO trial team members. This document underwent several review cycles to improve the communication flow between the two trial teams, with some specific procedures to follow within each team before escalating any issues to the Merck Serono CTL or the CRO project leaders. I was in charge of coordinating the review.

Results

As the timeframe of my internship took place during the very early start up of the study, no clinical trial result was available at the end of this 6-month period. Nevertheless, some strategic decisions were made within the trial team and within the company, to try to keep the
study start-up within the initial timelines, quality and budget. However, it is important to mention in this part some of the results we obtained during the start up.

1. Study documents: protocol and ICF

   As the coordinating author of the ICF, it was my responsibility to determine appropriate timelines for review within the trial team and to consolidate the comments from the trial team before sending the revised versions to the CRO. After receiving the comments form the different reviewers, I integrated them in the master ICF, with the support of the relevant functions when needed. The final version of the ICF and the HIPAA form are expected to be released only once the protocol will be finalized.

   The CRO is responsible for the translation in the different local languages, as well as for ensuring that local requirements are met by performing any local required modification.

   As a reviewer of the protocol, I had to provide our research scientist with my comments, so that she could implement them in the protocol or address them to the relevant function. I also had to ensure the consistency between the protocol and the ICF.

2. Outsourcing

   The decision of outsourcing had been made by the company before the timeframe of my internship. The CRO was in charge of the country and site feasibility, site selection process and site monitoring and management, the electronic Case Report Form (eCRF) programming and set-up, the central laboratory and other vendors management, writing all the study related documents (protocol, ICF, communication plan, monitoring plan, laboratory manual...)

   During my internship, as an active member of the trial team, I had to liaise with the CRO project leaders on a daily basis, for all the activities I was delegated by the CTL, such as, but not limited to, the communication plan review, the ICF review, the study aids (subject diary card and emergency card) drafting...

   A surveillance plan has been set-up within the trial team to have an overview of key CRO delegated tasks for the study. This document is planned to be for internal use only within the company, and allows the trial team to have an overview of the whole study progress and challenges. I have also been delegated the task of creating and drafting a template of this document during my internship.

3. Sites feasibility and selection

   At the end of the feasibility a country split between Alpine I and II has been performed, based on the recruitment potential of each country, and avoiding the competition between the two studies within a country.

   The sites contacted were asked to fill in an online survey to determine interest and initial site qualification, and the results were reviewed by the CRO feasibility specialist. Merck Serono trial team were provided on a weekly basis with a global update, and on a monthly basis with a detailed feasibility update, including the reasons for selection or non selection of the investigational site. This detailed update was shared with the affiliates in the different regions were the feasibility was conducted, to evaluate the feasibility results and to provide comments on the selected sites.

4. Expected recruitment

   The initial assumption was to have the first patient screened in September 2010, and the first patient randomized in October 2010. However, given the complexity of the feasibility and the strategic decisions made by the company, we had to review the initial timelines, and as of
July 2010, the first patient screened was planned for March 2011. The recruitment is expected to be completed over 2 years, until April 2013.

**Discussion**

1. **Trial methodology**

   As atacicept does not have proven efficacy in lupus patients yet, and placebo treatment alone cannot be justified for one year in SLE subjects with active disease, it is necessary to add atacicept/placebo onto SoC treatments. For most of the SoC drugs for lupus, there is no known effect size. This means that the trial must show superiority with the use of the study drug, and not just non-inferiority to SoC.

   The primary endpoint is based on the previously used composite endpoint (SLE responder index) used in registration trials for a similar drug in development, belimumab (the BLISS-52 and BLISS-76 trials) [4, 11]. It is appreciated by the lupus medical community that each of the currently most widely-used assessment tools (SELENA-SLEDAI and BILAG 2004 index) has strengths and weaknesses. SELENA-SLEDAI is useful for detecting improvements in subjects, whereas the BILAG 2004 index may be more sensitive at detecting worsening. The Physician Global Assessment (PGA) is incorporated to capture disease worsening that is not measured in the classic BILAG index. Atacicept targets BLyS and APRIL, and is foreseen to have either a similar or a higher efficacy compared to belimumab, which targets BLyS only. Hence, the use of an identical composite primary endpoint to that used in the belimumab phase III trials is appropriate.

   Secondary endpoints will assess specific outcome measures within the composite primary endpoint (BILAG, SLEDAI, PGA), and also critically important outcomes (to regulators and clinicians) that are not captured in this endpoint such as steroid-sparing effects. The morbidity from chronic steroid use is high, and is thus a focus of the results of studies in lupus. The major secondary endpoint focuses on endpoints that can bring additional label claims. This is why a hierarchical testing procedure is used. Corticosteroid sparing has been recently recognized in the draft EMEA guideline as a claim for SLE. Quality of life could also potentially be used in a label, although not explicitly stated as such.

   The expected responder rates and treatment effect size is based on the results of the belimumab trials. 12 % is approximately the average of the BLISS studies results (14% and 9.4%, respectively, for the 10 mg/kg dose arms). These studies were done in separate regions of the world, whereas this study will be conducted globally, and thus an average of the results was appropriate.

2. **Strategic decisions**

   2.1. **Outsourcing**

   The decision of outsourcing the study to a CRO is part of the strategy of the company. However, as the Sponsor of the trial, the company remains accountable for the conduct of all trial related activities, and thus the trial team has to oversee the trial and put in place some surveillance activities. Each the function within the trial team had to define how properly conduct the surveillance, in order to obtain a view on the outsourced activities.

   These surveillance activities are described in the surveillance plan. It was planned to be for internal use only. Nevertheless, as some of the surveillance aspects required specific tools and trackers, we decided to provide the CRO with a description of the trackers we would use, in order to be sure that we would be provided with the correct information to perform the surveillance.
This plan will be a living document that could be adapted at any moment during the study, if a trial team member feels that it is necessary for the study conduct, or when there is any recurrent issue that is not resolved in a timely fashion.

2.2. Protocol finalization and submission

The rationale to wait for the FDA’s feedback is based on the fact that the experts might make recommendations on this final draft, and this could lead to a protocol amendment in other countries, which would increase the budget of the study. However, as the study is based on the same design as the belimumab studies, we would not expect major comments from the FDA. This would also allow the company to obtain the FDA commitment to this program.

Due to strategic decisions from the company regarding the whole atacicept program, the final draft release has been delayed, and as of July 2010, it was planned to submit the protocol to the FDA in September. This delay will have an impact on the initial timelines for the submissions in the other countries.

2.3. Feasibility results

For the selection of the sites, we had to deal with some country specific requirements: the FDA requires that 25% of the patients included are from the US and China authorities required the inclusion of 300 Chinese patients in this phase III program, which is 1/3 of the overall patient number. Based on these requirements, the centres had to be selected accordingly.

In early June, it was decided by the company to start only one phase III study for the time being. Due to the country specific requirements mentioned above, this strategic decision had an impact on the sites to be selected. As a result the CRO re-evaluated the countries to be included in this single study based on recruitment potential, timelines etc, and increased the number of sites selected in some countries.

2.4. Communication plan

This document underwent 3 cycles of review within Merck Serono trial team. Following an audit of the CRO processes by Merck Serono, one of the findings was that the communication plan for the study needed to be adapted to complement the particular model of outsourcing used for this study. As of July 2010, the final document was still under revision within both parties.

Conclusion

This internship within Merck Serono gave me the opportunity to be involved in a global phase III program. The start-up of a study remains a critical period that can affect the overall quality, timelines and budget of the study, and thus affects the main objective for the company (launching atacicept on the market). In a highly competitive landscape such as the one in SLE, and with strategic decisions from the company, each decision had an impact on the start-up of this phase III program and resulted in a delay in the initial expected date of launch.

As a support of the CTL, I had the chance to work closely with the different functions within Merck Serono GCO, and in collaboration with a CRO. I have been delegated a lot of various tasks in addition to those described in this report and I was an active member of the trial team. This cross-functional role gave me the opportunity to integrate this team very quickly, to learn how to properly conduct the start-up of a global study, and to fully express my pro-activity. As a result of all that I have shown to the team, I have been offered a position in the CTM department and from August, 1st I am acting as Associate Clinical Trial Manager.
Bibliography


## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>APRIL</td>
<td>A Proliferation-Inducing Ligand</td>
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<tr>
<td>BILAG</td>
<td>British Isles Lupus Assessment Group 2004 Index of Lupus Disease Activity</td>
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<tr>
<td>BLyS</td>
<td>B-Lymphocyte Stimulator</td>
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<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
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<td>CTL</td>
<td>Clinical Trial Leader</td>
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<td>CTM</td>
<td>Clinical Trial Management</td>
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<tr>
<td>DBPC</td>
<td>Double-Blind Placebo-Controlled</td>
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<tr>
<td>DQA</td>
<td>Development Quality Assurance</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<td>GCO</td>
<td>Global Clinical Operations</td>
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<td>HA</td>
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<tr>
<td>HIPAA</td>
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<td>Health Related Quality of Life</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>PGA</td>
<td>Physician’s Global Assessment</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
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<tr>
<td>SELENA-SLEDAI</td>
<td>Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index</td>
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<td>SLE</td>
<td>Systemic Lupus Erythematosus</td>
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<td>SLICC</td>
<td>Systemic Lupus International Collaborating Clinics</td>
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<tr>
<td>SoC</td>
<td>Standard of care</td>
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<tr>
<td>TACI</td>
<td>Transmembrane Activator, Calcium-modulator and cyclophilin-ligand Interactor</td>
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<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
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Appendices

**Appendix 1:** atacicept is a recombinant, fully human fusion protein

Extracellular domain of TACI receptor  
(binds BLyS & APRIL)

Fc domain of human immunoglobulin  
(increases the stability of the molecule)

**Appendix 2:** Trial Design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background medication stable</td>
<td>Corticosteroids: Adjustable, Reduction encouraged</td>
</tr>
<tr>
<td>SELENA-SLEDAI ≥6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo QW</td>
</tr>
</tbody>
</table>

Week: -3 0 1 2 4 8 12 16 20 24 32 40 48 52

Safety Follow-up  
(for subjects withdrawn from trial medication or who complete 52-week treatment period without entering extension trial)

Extension Trial

QW=once weekly