Use of Chemokine (C-X-C Motif) Ligand 9 (CXCL9) as a Biomarker of Acthar Efficacy
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Questcor Clinical Investigator Initiated Study (IIS) Proposal Guidelines

Study Title:	Use of Chemokine (C-X-C Motif) Ligand 9 (CXCL9) as a Biomarker of Acthar Efficacy
Protocol Version and Date:	Protocol V2 January 21, 2026
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Please submit by email this completed IIS Proposal along with your ***curriculum vitae*** to your MSL.

A. SPECIFIC AIMS

In this study, we will test whether Acthar gel's anti-inflammatory properties modulate immune cells and lead to decreases in blood biomarkers and improvements in clinical parameters. Specific Aim 1 will examine levels of our predictive biomarker, chemokine (C-X-C motif) ligand 9 (CXCL9), and related transcripts, and determine whether they decrease in patients over time while taking Acthar. Specific Aim 2 will test whether the biologic changes measured in blood correlate with clinical markers, including lung function and symptom scores. Since we previously found that CXCL9 predicts clinical course, we hypothesize that CXCL9 transcript levels in blood will decrease over time in pulmonary sarcoidosis patients whose clinical outcome measures improve with Acthar.

B. BACKGROUND AND CLINICAL SIGNIFICANCE

We previously found that whole blood transcript levels of CXCL9 predicted pulmonary disease progression in sarcoidosis. (1). CXCL9 is an interferon-gamma (IFN-γ) inducible chemokine that participates in recruitment of T-effector lymphocytes to the lungs in sarcoidosis. Therefore, blood levels of CXCL9 reflect IFN-γ-driven inflammation and may serve as a surrogate biomarker for therapeutic response. Improvement in clinical response should be reflected by decreasing CXCL9 expression. Potential applications include: (1) identification of patients at higher risk for progression who may require more aggressive therapy, and (2) monitoring of disease response using CXCL9 expression levels.

C. RESEARCH DESIGN AND METHODS

Study Type/Design: The study design is an open label prospective trial.

Endpoints: Primary endpoint: A fall in *CXCL9* levels by 50%.

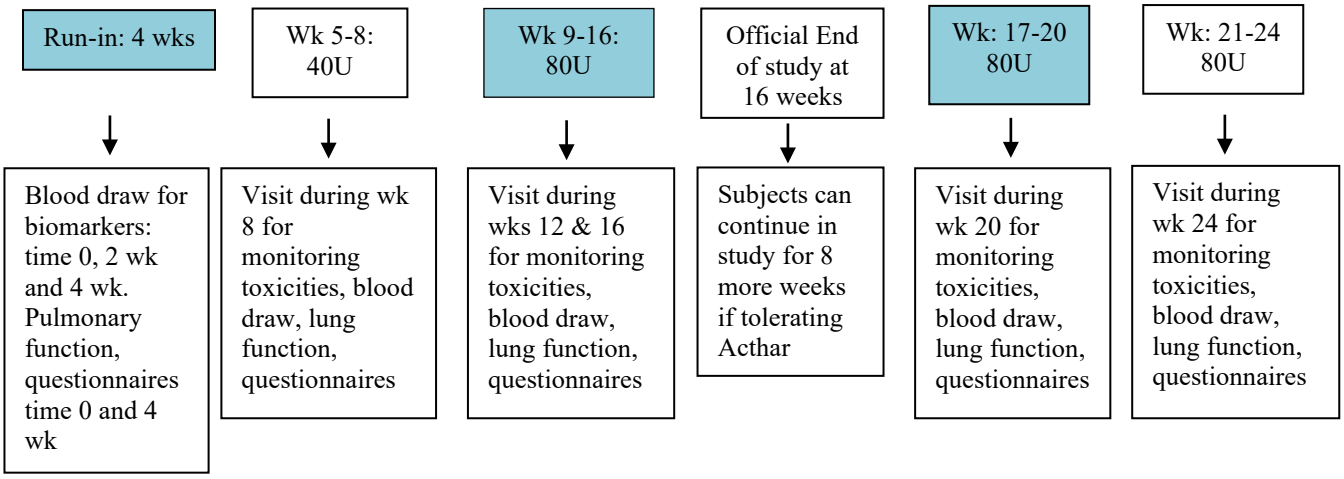
Secondary end-points: Improvement in forced vital capacity (FVC) by at least 5% predicted and improvement in dyspnea score measured by the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ).

Patient Recruitment: The study will be conducted at the University of California San Francisco (UCSF). Recruitment will occur through the UCSF Sarcoidosis Clinic, an ongoing longitudinal sarcoidosis cohort, collaborating pulmonologists, and National Institutes of Health (NIH)–sponsored sarcoidosis studies including the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study.

Subject number, target population, Inclusion and Exclusion criteria: Patients must have biopsy-proven sarcoidosis as defined by the joint American Thoracic Society / European Respiratory Society (ATS/ERS) Task Force. Eligible participants will be between 18 and 65 years of age.
Exclusion criteria include chronic illnesses other than sarcoidosis, including malignancy, chronic viral infection, chronic inflammatory conditions, tuberculosis, significant coexisting lung disease, or current tobacco use.
Participants must have an indication for pulmonary therapy with prednisone or a second-line agent such as methotrexate and demonstrate lack of improvement after at least three months of therapy based on symptoms, pulmonary function testing, or medication intolerance.

Treatment Overview*.* Patients will be screened verbally and medical records reviewed by the Principal Investigator (PI). Immunosuppressive medication doses must be stable for at least one month before enrollment and throughout the study.
Acthar gel will be administered according to the package insert: 40 units (U) intramuscularly (IM) or subcutaneously (SQ) every 72 hours, with escalation to 80 U as tolerated.

Study Design: A four-week run-in period will include blood collection at weeks 0, 2, and 4. Baseline pulmonary function testing and questionnaires will be performed at week 0.
Acthar will begin at week 4 at 40 U IM or SQ every 72 hours. After four weeks, the dose will increase to 80 U IM or SQ every 72 hours. Follow-up visits will occur at weeks 8, 12, and 16. The formal study ends at week 16, with an optional extension to 24 weeks.



Dosage and Administration of Acthar *Daily /weekly dose, administration, frequency:* Acthar will be initiated at 40 U of Acthar gel IM or SQ twice a week and escalated according to the figure above.

Laboratory Testing and Study Schedule The determination of *CXCL9* levels in each enrolled subject will be studied using a standardized quantitative polymerase chain reaction (qPCR) that will include samples from patients in the prior longitudinal cohort as well as positive controls we previously published (3, 4). This will ensure measurement accuracy of *CXCL9* throughout the study duration. The project will test a novel biomarker in sarcoidosis, *CXCL9*, (1) and its ability to detect disease response after therapy with Acthar in patients with moderate to severe pulmonary sarcoidosis. In addition, this biomarker will identify which patients are most likely to respond to Acthar. This study also has the capacity to measure related markers that may be useful in future studies of Acthar. These include other transcriptional markers we have identified in blood (3) as well as protein levels for CXCL9, CXCL10, and CXCL11 (manuscript in preparation). CXCL11 is particularly interesting as an immune modulator based on recent published data, and we have found that only ½ of our longitudinal cohort of patients showed induction of it, even though CXCL9 and CXCL10 were elevated. This suggests that CXCL11 may be another biomarker allowing better phenotyping of patients that show enhanced response to Acthar gel.

Patient Monitoring and Evaluation *Contingencies for patients not responding (i.e. dose adjustment, schedule change)*: According to the experience of clinical trial NCT# 02188017, which is another study assessing the efficacy of lower dose Acthar gel in pulmonary sarcoidosis, we will be initiating therapy at the stated dose of 40 U IM or SQ every 72 hrs. However, The PI of this study in reference noted efficacy at 80U which is also an FDA-approved treatment dose and given that we don't know at what dose Acthar may be more efficacious at reducing sarcoidosis inflammation and biomarkers, we have built into our study design a way to look at both doses within the same subject, rather than be forced to increase the dose in patients not responding to 40U of Acthar and complicating the study design.

Potential Pitfalls and Contingencies. In the study of any drug, the investigators must follow patients closely and patients must have access to the study physicians and staff. From the clinical perspective, we will provide close clinical follow up to monitor any side effects as early as possible and adjust medication dose as necessary. We will also reach out to other expert investigators with experience using Acthar gel for important advice if necessary. We are aware that patients taking higher dose Acthar gel may develop lower extremity edema and respond to treatment with aldactone. We will be prepared for such side effects. Any complaints or symptoms reported by a patient thought to be a side effect or adverse reaction will be reported to Questcor and the Committee on Human Research following all guidelines set forth by these entities.

Data Processing and Analysis

Statistical /Analytical Plan *Include data management and quality assurance*

There will be several types of data collection and processing in this study.

1. Clinical data: this includes data collected from the patient about their medical diagnosis, their medications, and allergies. Also, data necessary to confirm eligibility will need to be collected. In addition, PHI will be collected so that we can contact the patient. Each patient will be given a unique patient identifier that is not traceable to their PHI. This will be their unique ID number and used instead of PHI whenever possible. During study visits, data related to symptoms, questionnaires, and physical exam findings will be collected. This data will be stored on a secure UCSF server and network, and contained within a database created for the study. Any paper-related records will be stored in a locked cabinet per the UCSF Committee on Human Research standards. Data will be collected by the study PI, Dr. Koth, and the study coordinator, Sara Sun. Dr. Koth has more than 15 years of research experience and Mrs. Sun has more than 4 years of experience. Data integrity is assessed by periodic monitoring by the data manager, Mrs. Sun (checking that the data 100% matches the source).
2. Biologic data: this study also consists of collection of biologic samples that will be processed immediately. All study biologic samples will be labeled using the unique study ID. A biorepository database will be constructed for this study to keep the biologic samples. Samples will be processed to measure the transcriptional signatures

described above. Samples will also be analyzed for protein expression levels. Quality assurance will be performed as outlined above by analyzing appropriate negative and positive controls with each batch of samples.

Sample Size Justification

Using data from our previous manuscript, we have calculated that enrollment of 14 patients who meet the study criteria of worsening disease would be needed to reach our primary endpoint (α level P=0.05, power 80%).

D. REGULATORY, SAFETY AND MONITORING

Subject follow-up: The proposed study is 16 weeks, with an optional extension to 24 weeks. Subjects will be asked to follow-up in the UCSF Sarcoidosis Research Program every 2 weeks for the first month and then monthly until the end of the study (see diagram).

Removal of subjects from study: There are several unanticipated factors that would call for a removal of subjects from the study and include:

- Failure to report to follow up visits for monitoring
- Lack of adherence to Acthar gel
- Severe side effects leading to intolerability of Acthar gel
- Development of one of the exclusion criteria during the study enrollment phase
- Inability to perform study procedures
- Development of an adverse event of a degree to warrant removal from the study

Safety reporting, and other mandates.

This study will follow all safety and reporting procedures detailed below and approved by the IRB at UCSF (aka the Committee on Human Research). In addition, this study will register with ClinicalTrials.gov and update information as requested.

Frequency of adverse event monitoring: Adverse events will be monitored by the Clinical PI (Dr. Koth) in real-time. In addition, AEs will be reviewed monthly in the regularly scheduled QA meeting of UCSF Airway Clinical Research Center, which is attended, by Drs. Koth, Fahy, Woodruff, Lazarus and Boushey.

Types of Adverse Events:

• Expected Adverse Event is an AE that may be reasonably anticipated to occur as a result of the study procedures or study participation as described in the current CHR application or informed consent document.

• Unexpected Adverse Event. An AE defined as being unexpected if the event exceeds the nature, severity, or frequency described in the current CHR application or consent form. An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to an overdose of study medication, or
- Due to a deviation from the CHR approved study protocol

• Serious Adverse Event (SAE) is any AE that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience,
- Inpatient hospitalization,
- Persistent or significant disability/incapacity,

• Congenital anomaly/birth defect, or cancer,
• Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
• Event that changes the risk/benefit ratio of the study.

AEs will be reported to the local Institutional Review Board (the UCSF Committee on Human Research) in accord with the following guidelines:

Guidelines for Adverse Event Reporting		
Type of Adverse Event or Safety Information	Reporting Frequency	Format
AEs determined to be unrelated to research participation (one exception is unrelated deaths)	Not reported to CHR	These events are documented, referenced, and retained in the PI's study files for follow-up
AEs that are Definitely, Probably or Possibly related to research participation *AND* Serious or Unexpected	Reported to CHR within 10-working-days of UCSF PI awareness.	10-Working-Day Internal Reporting Form

Relationship to study participation is judged as follows:

- Definitely Related: An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.
- Probably Related: An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
- Possibly Related: An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
- Unrelated: The cause of the AE is known and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality then the event must be assessed as possibly related to research participation and reported to the CHR as indicated. Often, the cause of an unrelated AE is disease progression.

Reporting to other parties

The UCSF CHR reviews reports of AEs submitted by the PIs and determines whether an event meets the definition of an Unanticipated Problem involving risk to participants or others (UP). The CHR reports all UPs to the DHHS Office for Human Research Protection (OHRP), appropriate University and affiliate officials, and to the study sponsor. Unanticipated Problems (UPs) are defined as problems involving risk to participants or others which are unexpected,

research-related events that result in, or indicate a potential for, a significant risk to enrolled or potential participants or others, and necessitate corrective action or modification of the conduct of study activities.

II. Describe publication plan and anticipated number of abstracts and manuscript submissions (include intended conference(s) for presentation and month, year of conference(s)):

Before the study commences, I anticipate there would be one manuscript describing the study design and clinical data collected and at least one but likely several more describing the biological data measured after the close of the study.

F. REFERENCES

1. Su R, Li MM, Bhakta NR, Solberg OD, Darnell EP, Ramstein J, Garudadri S, Ho M, Woodruff PG, Koth LL. Longitudinal analysis of sarcoidosis blood transcriptomic signatures and disease outcomes. The European respiratory journal 2014.

2. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, Albera C, Brutsche M, Davis G, Donohue JF, Muller-Quernheim J, Schlenker-Herceg R, Flavin S, Lo KH, Oemar B, Barnathan ES, Sarcoidosis I. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. American journal of respiratory and critical care medicine 2006; 174: 795-802.

3. Koth LL, Solberg OD, Peng JC, Bhakta NR, Nguyen CP, Woodruff PG. Sarcoidosis blood transcriptome reflects lung inflammation and overlaps with tuberculosis. American journal of respiratory and critical care medicine 2011; 184: 1153-1163.

4. Su R, Li MM, Bhakta NR, Solberg OD, Darnell EP, Ramstein J, Garudadri S, Ho M, Woodruff PG, Koth LL. Longitudinal analysis of sarcoidosis blood transcriptomic signatures and disease outcomes. The European respiratory journal 2014; 44: 985-993.