Open Label Study to evaluate Efficacy and Safety of Short-Term, Adjunctive Adrenocorticotropic Hormone (ACTH) Gel Therapy in Rheumatoid Arthritis.

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Trial design: open label for 12 weeks

Dose/Route/Regimen: ACTHAR gel 80u subcutaneously twice weekly

Target population: 20 refractory adult Rheumatoid arthritis patients

Glossary of terms in protocol:

RA = rheumatoid arthritis

CDAI = clinical disease activity index

DAS = disease activity score

ESR = Erythrocyte sedimentation rate

CRP = C-reactive protein

A. Background and Rationale:

Adrenocorticotropic hormone (ACTH) gel (repository corticotropin injection) (ACTHAR) is a long-acting full sequence ACTH that includes other pro-opiomelanocortin peptides (1-6). ACTH is thought to have anti-inflammatory prospects as well as immunomodulatory effects mediated through melanocortin receptors (2). ACTH gel is FDA approved for several immune-mediated disorders including rheumatoid arthritis (RA), multiple sclerosis, systemic lupus erythematosus, polymyositis, nephrotic syndrome, and infantile spasm syndromes (1-6).

RA is a chronic systemic autoimmune inflammatory arthropathy of unknown etiology (7). The worldwide prevalence is approximately 1% of adults of all races. Disease onset occurs most often between the ages of 20 and 60 years, with peak occurrences at 50 to 60 years. The prevalence of RA varies with sex and age, and is higher in women than in men. Affected subjects experience considerable morbidity, including symptoms such as joint stiffness, pain and swelling, rapid loss of function, joint destruction, permanent deformity as well as a reduced life expectancy.

The treatment of RA has seen a dramatic paradigm shift over the past decade with the introduction of biologic response modifiers (5 that inhibit tumor necrosis factor, 1 inhibitor of interleukin-1, 1 that blocks interleukin-6, 1 that inhibits B-cells, and 1 that blocks co-stimulatory pathways), plus most recently an oral agent that blocks Janus

Kinase pathways. In addition, treatment with standard oral medications such as triple oral disease modifying drugs (DMARDs) also are effective options (7). Despite these advances, a large percentage of our patients require daily therapy with oral prednisone and/or don't respond to these current therapies. Thus, safe new therapies are still needed for this common immune-mediated inflammatory disease.

B. Hypothesis and Specific Aims:

Hypothesis: Patients with RA, who are receiving stable doses of background medications will have an improvement in disease activity (as measured by CDAI) when treated with 12 weeks of subcutaneous ACTHAR.

Specific aim 1: To determine the efficacy and safety of ACTH gel in refractory RA patients.

Specific aim 2: To determine the potential mechanisms of action of ACTH gel, pending review of efficacy data.

C. STUDY Design:

The proposed trial design would be open-label with a subcutaneous dose of ACTHAR 80 units, twice a week, for 12 weeks. The entry criteria would be:

1. RA diagnosis by ACR criteria
2. Active disease (CDAI > 10) (8, 9, 10)
3. Have received at least are biologic agent for at least 6 months

4. May or may not be receiving oral daily steroids (less than or equal to 20 mg/day) of prednisone equivalent
5. No current active infections requiring antibiotics
6. Patients must be on stable doses of RA therapies (e.g., methotrexate or other RA therapies for at least 4 weeks prior to baseline visit)

Table 1. Proposed Study Visits and Study Activities

	Screening	**Baseline**	**2wk**	**4wk**	**8wk**	**12wk**	**16wk**
Informed Consent	**X**						
Dispense medication		**X**		**X**	**X**	**X**	
Clinical Labs*	**X**		**X**	**X**	**X**	**X**	**X**
AE Monitoring			**X**	**X**	**X**	**X**	**X**
Efficacy assessments		**X**	**X**	**X**	**X**	**X**	**X**
Research Labs (PBMC's, serum, plasma, RNA)		**X**	**X**	**X**	**X**	**X**	**X**

*CBC, glucose, creatinine, ESR, CRP, ALT

Patient population and estimated sample size: Patients will be recruited from UPMC Rheumatology Outpatient Clinics. A pilot study of 20 patients will provide initial information on efficacy of this agent in refractory RA patients. For the year ending in Spring 2012, we had over 4,000 unique, active RA patients in our outpatient clinics. We have 35 Rheumatologists who practice at UPMC in Western, PA.

Primary end-points:

1. Changes in CDAI at week-12 (9); we propose a 20% improvement after 12 week of therapy compared to baseline as a positive response.

Secondary end points:

1. Changes in DAS28-CRP (9, 10)
2. Changes in acute phase reactants (ESR, CRP)
3. Changes in fatigue, as measured by FACIT (11).

D. Data Analysis:

We will determine the frequency of subjects who have at least a 20% improvement in CDAI from baseline to week 12 visit. We will document the frequency and events of adverse event. For secondary endpoints we will also determine frequency of subjects what have at least 20% improvement in DAS28-CRP, fatigue, ESR and CRP from baseline to week 12.

E. Data captured and Database:

The Division of Rheumatology and Clinical Immunology has experience spanning four decades in the development, maintenance and refinement of disease-specific databases of longitudinal cohorts of patients with rheumatic diseases. In the past few years we have developed a web-based database that we plan to use for this investigator-initiated trial. The key characteristics of the Rheumatic Disease Musculoskeletal System (RDMS) are: **1)** the ability for longitudinal data collection and database management of data

from multiple clinic visits; **2)** the ability to use multiple methods of data entry (e.g., web-based, tablet-based, or manual from hard copy) that permit secure data collection at various UPMC clinics, other institutions or Academic Medical Centers; **3)** data capture and synthesis in real-time has the ability to provide immediate feed-back to clinic staff and patients with regards to the data collected and trends over time; **4)** flexibility to meet the needs of diverse researchers and their research questions through a modular design allowing for customization of data collection specific to individual study questions; **5)** adaptability for future research studies through the addition of new forms or disease-specific modules; **6)** easy accessibility of data for analysis by research team members with limited programming and statistical training such as coordinators, fellows and faculty; **7)** capability for automated downloading and database integration of discrete well-defined clinical data, such as medication data, laboratory data and imaging data, from other electronic UPMC systems (e.g., EPIC electronic medical record system, Medical Archival Record System (MARS)); **8)** patient data is separated into different data modules (e.g., Health Insurance Portability and Accountability Act (HIPAA) identifiers, demographic information, generic connective tissue disease data and disease-specific data) with restricted user access and linkage between the HIPAA information and other data based on a unique 8-digit subject ID number; **9)** a set of common definitions for terms and data collection forms used in the database and the establishment of a committee to oversee the common definitions and forms; and **10)** a research biospecimen and sample tracking system module.

F. Exploratory future objectives:

Once the clinical trial is completed we will consider what mechanistic studies to pursue. We plan to collect appropriate samples and store in -80% freezer in one of the Rheumatology Division's freezers.

G. Proposed time line:

Estimated time line (including IRB approval, study initiation, enrollment, study completion and submission of publication):

2 year trial

- 6-month start-up (develop forms; IRB submission)
- 18-month recruitment and follow-up

H. References:

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