An Open-Label Pilot Study of ACTH in the Treatment of IgA Nephropathy at high risk of progression

NCT# 02282930

March 11, 2015

STUDY TITLE:

An Open-Label Pilot Study of ACTH in the Treatment of IgA Nephropathy at high risk of progression

Study Drug

ACTH (Acthar gel®)

Study Phase

Phase III

Support Provided By

Mallinckrodt Pharmaceuticals Inc.

Sponsor Investigator/Institution

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Mayo Clinic, Rochester, MN

Research Coordinator

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Signature Page

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We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

The Principle Investigator at local site: _____ Print name	 _____ Signature	 __ __ / __ __/ __ __ __ __ Date
Primary Principle Investigator: Dr. Fernando Fervenza, M.D., Ph.D _____ Print name	 _____ Signature	 __ __ / __ __/ __ __ __ __ Date

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1.0 INTRODUCTION

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures. This study will be coordinated at up to four additional sites in addition to Mayo Clinic Rochester.

1.1 IgA Nephropathy Background:

Immunoglobulin A nephropathy (IgAN) is an immune-complex mediated glomerulonephritis characterized by deposition of polymeric IgA in the mesangium of the kidney.[1] It is the most common form of primary glomerulonephritis worldwide and is prevalent amongst all ages and racial demographics.[2] Its pathogenesis has been under investigation for the last several decades and one of the key players is the aberrant glycosylation pattern of IgA1. There is now convincing evidence that the hinge region of IgA1 heavy chain has defective glycosylation with a reduction in the galactose and or sialic acid residues.[3] As a result the *N*-acetylgalactosamine in the IgA1 hinge region is exposed and recognized by IgG antibodies. This in turn leads to formation of IgG-IgA immune complexes and their deposition in the mesangium and renal injury that subsequently ensues.[4-7]

The renal outcomes of IgAN vary significantly between individuals ranging from minimal proteinuria and stable renal function to development of endstage renal disease (ESRD) in up to 50% of the cases.[8] Markers of poor prognosis include impaired kidney function at presentation, hypertension and persistent proteinuria > 1 g/24h.[9,10] In addition, the recent Oxford classification has identified MEST (mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis) as an independent indicator of poor renal outcome.[11] Despite the prevalence and severity of IgA nephropathy, there is little consensus as to the most effective therapy. To date, the most effective therapies for IgAN appear to be angiotensin converting enzyme inhibitors (ACE-I), corticosteroids, and omega-3 fish oil supplements that contain a high concentration of Eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). Other therapies including tonsillectomy and cytotoxic medications have been used in patients with IgAN with variable success. [12-18] In some patients renal disease progresses despite treatment and thus a search for additional forms of therapy is ongoing.

While glucocorticoids and alkylating agents can successfully treat IgAN and other forms of primary glomerulonephritis, prolonged treatment with these agents is associated with significant clinical toxicities. Glucocorticoids are associated with steroid-induced diabetes, avascular necrosis of the hips and shoulders, excessive weight gain, osteoporosis, and increased risk for infectious complications.[19-21] Cyclophosphamide has been used in combination with corticosteroids in the treatment of patients with IgAN with high-risk features.[15] While alkylating agents allows clinicians to reduce the amount and duration of steroid therapy, only 20-40% of patients achieve a complete or partial response. Moreover, repeated use of cyclophosphamide

and other alkylating agents is associated significant toxicity including premature ovarian failure and increased incidence of secondary malignancies.[22-25]

1.2 ACTH Background:

H.P. Acthar® Gel (ACTH) is obtained from processing of the porcine pituitary gland and is currently the only FDA approved therapy for the treatment of nephrotic syndrome. The active ingredients in H.P. Acthar® Gel are part of the family of structurally related peptides known as melanocortin peptides. Melanocortin peptides, which include adrenocorticotrophic hormone (ACTH) and the α-, β-, and γ-melanocyte stimulating hormones, are derived from the natural protein pro-opiomelanocortin (POMC) and bind to the cell surface G-protein coupled receptors known as melanocortin receptors (MCRs).[26,27] To date, 5 forms of MCRs have been cloned, each with different tissue distributions, affinities, and physiological roles. Although the functional roles of all the peptides in H.P. Acthar® Gel have not been fully elucidated, ACTH is known to have activity at all 5 MCRs.

H.P. Acthar Gel has steroidogenic mechanisms of action through endogenous production of cortisol and is reported to have immunomodulatory properties facilitated through interactions with melanocortin receptors found in immune effector cells and other tissues. MCRs are expressed in glomerular podocytes and receptor stimulation has been demonstrated to reduce oxidative stress and improve glomerular morphology by diminishing podocyte apoptosis, injury and loss in the remnant kidney animal model.[28] Inhibition of nuclear factor-kB (NF-kB) signaling is a key anti-inflammatory mechanism of melanocortin peptides.[29] NF-kB controls the expression of many genes, including pro-inflammatory cytokines, cytokine receptors, chemokines, growth factors, and adhesion molecules, and modulation of NF-kB is a main mechanism behind the widespread and powerful effects of melanocortins on inflammatory pathways.[30]

Apart from its anti-inflammatory effects, humans data also supports an anti-proteinuric effect in addition to a pronounced lipid-lowering effect in healthy individuals,[31] in steroid-treated patients with renal disease[32] and in hemodialysis patients[33], using a similar synthetic ACTH preparation that is not available in North America. More recently, using H.P. Acthar® Gel (ACTH) we were able to demonstrate a significant benefit in patient with Membranous Nephropathy.[34] Twenty patients received a subcutaneous dose of 40 or 80 IU twice weekly. Baseline characteristics included mean proteinuria (9.1±3.4 g/day), albumin (2.7±0.8 g/dL), estimated glomerular filtration rate (77±30 ml/min) along with elevated total and LDL cholesterol. By 12 months of follow-up, there was a significant improvement in proteinuria in the entire cohort, decreasing to 3.87±4.24 g/day ($p<0.001$) with significant improvements in serum albumin, total and LDL cholesterol. A > 50% decrease in proteinuria was noted in 65% of the patients with a trend towards better outcomes among patients who received greater cumulative doses. No significant adverse effects were documented.

Similarly, a recent pilot study showed benefit of Acthar® Gel (ACTH) in the treatment of Systemic Lupus Erythematosus (SLE).[35] Ten females (mean age = 49 year, disease duration = 7 years, with SLE were treated with ACTH Gel 80 U for 7-15 days and were assessed weekly for 28 days. Outcome measures included Physician and Patient Global Assessments, SLEDAI-2 K, Lupus Quality of Life scale, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, erythrocyte sedimentation rate, and C-reactive protein. Student's t-test compared data obtained at days 7, 14, and 28 with those from baseline. The primary endpoint of SLEDAI-2 K improvement was reached at all observation times ($p < 0.05$) and statistically significant improvements were observed for most other parameters. No treatment-related serious or unexpected adverse events were observed.

These results suggest that ACTH Gel may provide a novel anti-inflammatory and immunomodulatory treatment option with possible mechanisms of action beyond steroidogenesis. Considering that IgA nephropathy is an inflammatory glomerular disease, we hypothesized that adrenocorticotrophic hormone (ACTH) therapy in the form of HP Acthar® gel may reduce glomerular inflammation, improve podocyte survival and may provide an effective therapy in patients with IgA nephropathy and proteinuria.

1.2.1 Safety Profile

The Acthar Prescribing Information recommends the use of 40 to 80 U administered intramuscularly or subcutaneously every 24 to 72 hours in adults and children over 2 years of age; with the specific dosage individualized according to medical condition. Recent published use of Acthar in subjects with non-diabetic nephrotic syndrome included regimens of 80U 2 times per week and 40U 2 to 3 times per week for 6 to 14 months. Bomback et al demonstrated promising efficacy results with the 6 month regimen of 80U 2 times a week; the results were less impressive with a 6 month regimen of 40U 2 to 3 times per week.[36] Tumlin and colleagues reported promising results in an Investigator-initiated clinical trial of Acthar in subjects with diabetic nephropathy, which included Acthar regimens of 16U and 32U per day for 6 months, the original design for this present protocol planned to assess two Acthar regimens (40U 5 times per week for 24 weeks and 80U 2 times a week for 24 weeks) in treatment-resistant iMN patients.[37] As discussed above, we have used Acthar Gel 40 to 80U SC twice a week for up to 9 months with minimal side-effects. Thus, the Acthar 80U 2 times per week regimen for 6-months proposed in the present study is consistent with the indicated use of Acthar and is believed to have an acceptable risk/benefit ratio in this population.

The Acthar regimen will be administered as the solely immunosuppressive therapy. The dosing will begin and end with Acthar 80U 2 times per week and will continue through Week 24 (6 months). The 24 week regimen with a 24-week follow up was selected based on additional controlled studies in which subjects with nephrotic syndrome treated with modified release synthetic fragment ACTH(1-24).[34,36-38] Data from these studies show that a 6 month regimen demonstrated remission (partial or complete) after 6 months of dosing that was sustained after 6 months of follow-up.

1.3 Hypothesis and Rational for Study Design

Hypotheses: In patients with progressive IgA nephropathy, ACTH gel injection at a dose of 80 units subcutaneously **twice weekly for 6 months** is effective in inducing improvement in proteinuria and renal function.

2.0 OBJECTIVES

2.1 Primary Efficacy Endpoints:

Patients achieving complete or partial response as defined below:

2.1.1 Complete Response: At 12 months

- < 300 mg proteinuria/24 hours
- No greater than a **10% reduction** in GFR as determined by quantified creatinine clearance

2.1.2 Partial Response: At 12 months

- > 50% reduction in 24 hour proteinuria
- No greater than a **25% reduction** in baseline GFR as quantified creatinine clearance

2.1.3 No Response: At 12 months

- A ≤ 50% reduction, unchanged or increasing proteinuria over baseline levels will be considered no response
- A greater than a 25**% reduction** in baseline GFR as quantified creatinine clearance

2.2 Primary Safety Endpoints:

- Incidence of Infections: Defined as the development of pneumonia, complicated UTI/Pyelonephritis
- Glucose control – development of diabetes

2.3 Secondary Exploratory Efficacy Endpoints:

- Improvement in hematuria
  Categorical: <3 rbc/hpf; up to 20 rbc/hpf; 20 to 50; 50 to 100; >100 rbc/hpf

3.0 STUDY POPULATION

This study will be completed in IgA Nephropathy patients whom are at risk of progression.

3.1 Inclusion Criteria:

3.1.1 Renal Histology-Entry Criteria:

Note: All eligible patients will have undergone a renal biopsy compatible with a diagnosis of IgA nephropathy within **36 months** of study entry. The diagnostic criteria for IgA nephropathy are as follows:

- Diagnosis of IgA nephropathy on renal biopsy.

Clinical Criteria:

Age > 18 years old

- **Proteinuria > 1000 mg/24h** despite documented ACEi/ARB therapy and adequate blood pressure control for > 3 months
- Quantified **24h creatinine clearance** > 30 ml/min/1.73m2
- **Blood pressure** <130/80 mmHg at >75% of the readings.
- **Henoch Schoenlein Purpura (HSP):** Patients with biopsy proven IgA nephropathy and clinical features consistent with Henoch Schonlein Purpura will be considered eligible for the study
- Patient must be **able to receive injections** to be enrolled in the study
- Patient must have a **Kidney biopsy slide** on file- that can be sent to the Mayo Clinic.

3.2 Exclusion Criteria:

Patients with any of the following criteria will NOT be considered eligible for study participation

- Clinical and histologic evidence of IgA predominant Lupus nephritis
- Patients with greater than 50% glomerular senescence or cortical scarring on renal biopsy
- Serum Cr > 3.0 mg/dl or creatinine clearance GFR < 30 ml/min at the time of screening
- Patients with history of Crohn's disease or Celiac Sprue
- Clinical evidence of cirrhosis, chronic active liver disease
- Known infection with hepatitis B, hepatitis C, or HIV (patients will be serologically screened prior to study entry- *if the test has been completed in the last two years- the patient will not have to undergo additional testing.*)
- Active systemic infection with bacterial, viral, fungal, or mycobacterial or atypical mycobacterial infections (excluding fungal infections of nail beds)
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening
- Positive pregnancy test or breast feeding at time of study entry (urine pregnancy test will be performed for all women of childbearing potential no later than 7 days prior to treatment) or patients unwilling to comply with contraceptive measures as outlined above

- Patients receiving therapy with oral prednisone or glucocorticoid equivalent in the past 3 months
- Patients who had received immunosuppressive therapy including cyclophosphamide, MMF, cyclosporine, tacrolimus or azathioprine in the last 6 months
- Current or recent (within 30 days) exposure to any investigational drug
- Patients having received a live vaccine within 28 days of study enrollment
- Hemoglobin: **<** 8.5 gm/dL
- Platelets: **<** 100,000/mm
- AST or ALT **>**2.5 x Upper Limit of Normal
- Patients with anaphylaxis and/or known allergic reactions to ACTH
- Previous Treatment with ACTH
- History of drug, alcohol, or chemical abuse within 6 months prior to screening
- Concomitant or previous malignancies, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix
- History of psychiatric disorder that would interfere with normal participation in this protocol
- Significant cardiac or pulmonary disease (including obstructive pulmonary disease)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complication
- Inability to comply with study and follow-up procedures

4.0 STUDY DESIGN:

An Open-Label Phase III Study of ACTH in the Treatment of patients with IgA Nephropathy at high risk for progression. The study will be completed at the Mayo Clinic and a possible additional four sites. A total of twenty-one patients will be enrolled in the study. Up to ten participants in total may be enrolled by the potential sites outside Mayo.

4.1 Treatment Plan

Patients meeting all entry criteria for the study will be eligible to enroll in this phase III, open-label trial. The participants will be given ACTH injections for 6 months with an additional 6 months of follow up.

4.2 Treatment:

- HP Acthar® gel will be given in a dose of 80 units subcutaneously (SC) twice weekly for total of 6 months.

4.3 Test Schedule and Monitoring for ACTH Treatment (Clinical and Laboratory Evaluations)

Test Schedule

	1	2	3	4	5	6	7
Visits (month)		Day 0	1 mo	3 mo[A]	6 mo	9 mo[A]	12 mo/EOT
Study Phase	Screening	Baseline	Treatment			Follow up	
Window (days)	-14	+/-3	+/-3	+/-3	+/-3	+/-3	+/-14
History/Exam	x	x	x	x	x	x	x
Vitals	x	x	x	x	x	x	x
Drug Administration		x[e,f]	x	x	x		
Venipuncture Chg	x	x	x	x	x	x	x
CBC w/diff.	x	x	x	x	x	x	x
Metabolic Panel	x	x	x	x	x	x	x
Albumin	x	x	x	x	x	x	x
Glucose	x	x	x	x	x	x	x
Hemoglobin A1c	x[g]	x	x	x	x	x	x
Lipid Panel	x	x		x	x		x
HIV/Hepatitis B/C	x						
Pregnancy (urine)	x	x					x[D]
Optional Research labs: Biomarker study		x[B,C]		x[B,C]	x[B,C]	x[B,C]	x[B,C]
Optional DNA		x[B,C]					
Optional Biopsy Review							x
24 hour protein	x	x[B]	x	x	x[B]	x	x[B]
Creatinine Clearance	x	x[B]	x	x	x[B]	x	x[B]
Volume Measurement	x	x[B]	x	x	x[B]	x	x[B]
Urinalysis	x	x	x	x	x	x	x

A. At month 3 and 9, should fall on 'Standard of Care' visits- which means they will be considered 'expanded standard care visits'. This also means that the primary site (Mayo Clinic) will only be paying for the optional studies (if the patient is enrolled) and the 24 hour urine sample, which will be shipped.

B. Each visit the following will be shipped to the Mayo Clinic: 24hour Urines- Creatinine Clearance and Volume measurements, and optional research bloods for DNA and biomarker study. All others including the Urinalysis and panels will be performed at local sites.

C. Optional Research labs (including biomarkers in both urine and blood) will be from one10ml red top tube which the serum will be drawn and divided equally into five 1 mL cryovials to be frozen and stored. 50 mL of urine will be drawn from a random urinalysis collection and then will be processed and aliquoted to be frozen and stored. Two 10 ml EDTA tubes will be used for DNA extraction, and will be processed into 2 aliquots of white blood cells (buffy coat) and stored for future DNA extraction.

D. The urine pregnancy test will be completed at screening, and baseline. If the subject leaves the study early- an additional pregnancy test will be requested as a safety assessment.

E. The drug will be administrated by trained staff members as a training lesson for the patients. The patients are allowed to have a significant other take part in the lesson if the patient is unwilling or unable to administer the injection themselves.

F. Please note the patients will be requested to wait with the training staff for 30minutes after the drug is administered- i.e. a safety observation period.

G. If the patient has had a HIV, Hep B & C test in the last two years- this will count towards the study.

4.3.1 Screening Laboratory Data

If any of the exams, tests or procedures for the screening visit are completed as routine standard of care within 14 days of study enrollment, participants do not need to repeat them for the screening visit. It will be up to the study's Principal Investigator to review and consider if the previous findings are appropriate and adequate to use. If it is determined that the findings are not adequate the necessary items will be repeated for the screening visit. Additionally, if the screening data meets study inclusion criteria, the results will be used for the baseline visit as well to reduce the amount of blood draws for the patient.

Patients meeting the entry criteria and consenting to participate in the protocol will undergo a complete physical exam and undergo the following laboratory tests:

- Physical Exam
- Complete Metabolic Panel including glucose, BUN, creatinine, potassium, sodium, chloride, bicarbonate, total bilirubin, alkaline, phosphatase, total protein, albumin, SGOT (AST), and SGPT (ALT), calcium, phosphorus
- Lipid Panel including Cholesterol (serum- total), direct measurement, high density cholesterol (HDL), and triglycerides
- CBC with differential and platelets
- Hemoglobin A1c
- 24 hr urine collection for protein and creatinine clearance
- Urinalysis with microscopy
- HIV test (unless completed in the last two years)
- Hepatitis B and Hepatitis C screening (unless completed in the last two years)
- Urinary Pregnancy test if female
- Vital signs (including heart rate and blood pressure)

4.3.2 Baseline (Day 0) Laboratory Data

Patients meeting the entry criteria and consenting to participate in the protocol will undergo a complete physical exam and undergo the following laboratory tests:

- Baseline physical exam
- Complete Metabolic Panel including glucose, BUN, creatinine, potassium, sodium, chloride, bicarbonate, total bilirubin, alkaline, phosphatase, total protein, albumin, SGOT (AST), and SGPT (ALT), calcium, phosphorus
- Lipid Panel including Cholesterol (serum- total) , direct measurement, high density cholesterol (HDL), and triglycerides
- CBC with differential and platelets
- Hemoglobin A1c
- 24 hr urine collection for protein and creatinine clearance
- Urinalysis with microscopy
- Pregnancy test if female

- Biomarker studies: Blood and urine will be processed appropriately and frozen for future biomarker analysis. The specific biomarkers to be analyzed will be determined at a later time.
- DNA (Storage)
- Vital signs (including heart rate and blood pressure)
- Given Study Drug Diaries to complete

4.3.3 Follow Up Exam and Laboratory Assessment-month 1, 3, 6, 9, 12

- Physical exam and dictated office note will occur after 1 month and then every 3 months- Medical history and response to treatment with ACTH. Please note month 3 and 9 should be considered 'standard of care visits' because patients with IgA nephropathy at risk of progression need to be seen at least once every 6 months.
- Complete Metabolic Panel including- glucose, BUN, creatinine, potassium, sodium, chloride, bicarbonate, total bilirubin, alkaline, phosphatase, total protein, albumin, SGOT (AST), and SGPT (ALT), calcium, phosphorus
- Lipid Panel (included at month 3,6 and 12) including Cholesterol (serum- total), direct measurement, high density cholesterol (HDL), and triglycerides
- Hemoglobin A1c
- 24 hr urine collection for protein and creatinine clearance
- Urinalysis with microscopy
- Biomarker studies (except for month 1): Blood and urine will be processed appropriately and frozen for future biomarker analysis. The specific biomarkers to be analyzed will be determined at a later time.
- If agreed- the optional biopsy review will occur at the 12month visit
- Vital signs (including heart rate and blood pressure)

4.3.4 Study Discontinuation and Early Termination

- Pregnancy test (urine) for women of childbearing potential
- Physical exam and Medical history will be completed in response to treatment with ACTH
- Complete Metabolic Panel including- glucose, BUN, creatinine, potassium, sodium, chloride, bicarbonate, total bilirubin, alkaline, phosphatase, total protein, albumin, SGOT (AST), and SGPT (ALT), calcium, phosphorus
- Lipid panel including Cholesterol (serum- total), direct measurement, high density cholesterol (HDL), and triglycerides
- Hemoglobin A1c
- 24 hr urine collection for protein and creatinine clearance
- Urinalysis with microscopy
- Vital signs (including heart rate and blood pressure)
- Biomarker studies: Blood and urine will be processed appropriately and frozen for future biomarker analysis. The specific biomarkers to be analyzed will be determined at a later time.
- If agreed- the optional biopsy review will occur.

Detailed methods for specimen handling, collection, processing, shipping and storage will be provided in the Laboratory Manual provided by Mayo Clinic. All laboratory tests will be performed by the designated central laboratory.

4.4 Identification Number

The subject/identification number will consist of the patient's initials (First Middle and Last) along with the medication kit number. This number will be used to identify the subject throughout the study and will be entered on all study documents.

The study number will not be assigned to more than one individual. If a subject was not given a medication number, due to being excluded before a number had been assigned, the patient would be considered excluded with no issues in regards to number assignment. However if the subject was later deemed ineligible to receive the treatment or needed to discontinue from the study, the subject would have been assigned a medication number and therefore once they discontinue on the study- that number cannot be used by an additional individuals.

4.5 Optional Research Lab (Biomarkers)

4.5.1 Collection and Banking of Blood and urine for future testing at Mayo:

There has been a common antibody found in patients with vasculitis (ANCA) and in some patients with the diagnosis of membranous nephropathy (anti-PLA2R), which are example of diseases affecting the kidney. In the future similar antibodies may be found for in patients with IgA nephropathy. We would like to have the opportunity to test for those antibodies and any other markers related to IgA nephropathy that could be found in the future. Labels will be provided in advance by the Mayo Clinic.

- Optional Blood Sample (Baseline, 3, 6, 9 and 12 months)
    - o 10 ml of blood in a red top tube
    - o Let clot for 15-30 minutes at room temperature.
    - o Centrifuge 3000 RPMs at 4 degrees for 15 minutes
    - o Aliquot equally into 5 – 1ml tubes provided in advance by Mayo Clinic
    - o Freeze at -80 C

- Optional Urine Sample (Baseline, 3, 6, 9 and 12 months): 50 mL of urine will be drawn from a random urinalysis collection and will be processed and aliquoted to be frozen and stored.
    - Add 12 mL of the urine into 4 - 15 mL conical tubes
    - Add 15 µL of protease inhibitor to the half that will be treated with protease inhibitor and invert tube 5 times to mix.
    - Spin the tube (and its counterbalance) at 1000 g for 12 minutes.
    - Aliquot the treated and untreated supernatant equally into 4 - 5 ml aliquots each and store at –80 °C

Send all samples to Mayo Clinic upon patient's completion of Month 12's visit on 10 pounds Dry Ice.

4.5.1.1. Shipping

Shipping to be pre-paid by Fed Ex labels on Monday, Tuesday or Wednesday:

Biospecimens Accessioning and Processing (BAP) Freezers
Stabile SL-16
150 Third Street SW
Rochester, MN 55902

4.5.2 Optional DNA Testing

Recent data show that in a number of glomerular disease (e.g. membranous nephropathy) mutations in HLA alleles are associated with an increased risk for developing the disease.[39] The same has been proposed for IgA nephropathy.[40] Thus we would like to evaluate potential genetic mutations in this group of patients. We will ask for the patients consent to further evaluate this linkage by collecting samples of blood to perform additional testing as part of their informed consent form (ICF). The DNA sample would be taken at Baseline, but shipped with the additional biomarkers listed above.

- Two 10 ml EDTA tubes will be used for DNA extraction, and will be processed into 2 aliquots of white blood cells (buffy coat) and stored for future DNA extraction.

4.5.2.1 Quantitative gene expression analysis

Quantitative gene expression analysis using real-time PCR and Microarray technology in peripheral blood mononuclear cells: There is little information on global gene expression changes that occur during active nephrotic syndrome secondary to IgA nephropathy subsequent to remission of this disease. Furthermore, there is no information on how ACTH affects gene expression of potentially pathogenic genes. As part of this study, peripheral blood will be collected at Time 0, and 12 months after therapy. Following treatment with ACTH, B-cell-specific genes will be assessed to track the extent of treatment in the B-cell pool gene expression. Both quantitative TaqMan real-time polymerase chain reaction and gene microarray (Affymetrix U133 chips) will be used to evaluate gene expression profiles. Real-time PCR will be used only to confirm the findings of the gene chip for genes with statistical significance.

4.6 Optional Biopsy Review

4.6.1 Histopathology

Due to the expertise of the pathologists at each of the clinical centers and to the characteristic findings on the renal biopsy in IgA nephropathy a review of the biopsy slides will not be required prior to enrollment at a Central Pathology Laboratory. However, a report documenting the results of the histology review including, light microscopy, immunofluorescence and electron microscopy results, as well as percentage of global and segmental glomerular sclerosis, tubulo-interstitial index, and immunofluorescence findings will be submitted and reviewed by the study P.I prior to enrollment into the study.

At the end of the study, Renal pathology biopsy slides for the patients that consented to have their slides reviewed will be centrally reviewed by Dr. Sanjeev Sethi, from the Pathology Department at Mayo Clinic Rochester.

4.6.1.1. Shipping

Shipping to be pre-paid by Fed Ex labels on Monday, Tuesday or Wednesday:

Julie Allen
Department of Nephrology and Hypertension
Mayo Clinic, MA19-01-W2
200 First Street, SW
Rochester, MN 55905

5.0 Study Medication

5.1 ACTH dosage and administration

Approximately twenty-one (21) subjects will receive HP Acthar ®gel. The appropriate quantities of vials will be dispensed to each subject at each visit by the study team. Each dose will consist of 80 U/mg given as an injection at home by the patient or trained family member. The injection will be given twice a week for a total of six months (24weeks).

- Each Patient: 1.0 mL Acthar SC titrated to 2 times per week- dosing as follows:
    - **Week 1**: 1 injection (Day 0) will be completed in clinic- where the injection training will occur. Inject 2 will be completed by the patient or trained family member at home
    - **Week 2 to 24** (month 6): 2 injections per week (cannot be 2 consecutive days, but no more than 3 days apart).

5.1.1 Preparation for Administration: The patients will be given vials from the study coordinator who will pick them up from pharmacy. The vials will then by take home for self-injection. The 1.0 mL multi-dose vials will contain the 80 units per mL needed to complete one of the two doses per week.

5.2 Compliance Control

Subjects will be trained on the study medication dosing and must exhibit proper technique before leaving the injection 1 (on Day 0) teaching session. The subjects will also complete a dosing booklet and will bring it with ALL their medication vials to each visit. At each visit the subject's dosing booklet will be reviewed with the subject to discuss compliance and medication administration.

6.0 Investigational Product:

6.1 Clinical Study Materials:

The H.P. Acthar ® Get will be provided free of charge by the Mallinckrodt. The lot numbers and expiration dates (if available) will be supplied on the medication vials and will be recorded in a

drug dosing accountability log along with the number of vials returned empty and full. A record will also be maintained indicating the receipt and dispensation of all medication supplies. At the conclusion of the study, all used and unused study medication will be destroyed by the designated destruction facility.

6.2 Pharmaceutical Formulation

Acthar is a highly purified sterile preparation of prolonged-release ACTH in 16% gelatin for intramuscular or SC injection. Acthar contains 0.5% phenol, not more than 0.1% cysteine (added), and sodium hydroxide and/or acetic acid to adjust pH and water for injection. Acthar is obtained from processing porcine pituitary using a Food and Drug Administration (FDA) approved process.

6.3 ACTH storage includes Labeling and Packaging

H.P. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store H.P. Acthar Gel (repository corticotropin injection) under refrigeration between 2°-8°C (36°- 46°F). Product is stable for the period indicated on the label when stored under the conditions described.

Acthar will be labeled according to all applicable federal regulations.

6.4 Dispensing Procedures

Acthar will be supplied to the subject in kits containing the appropriate amount of vials. During the treatment phase the subjects will receive a new kit at each visit that will contain the appropriate number of vials to get the patient to the following visit.

7.0 Safety Assessments

7.1 Specification of Variables and Procedures

Safety outcomes will be assessed by treatment-emergent adverse events; physical examinations; laboratory measurements including 24-hour urine collections, glycemic status (HbA_{1c}), hematology, chemistry (includes serum glucose) and urinalysis, blood pressure (seated), and heart rate.

The following will also be completed as per the Schedule of Procedures

- A complete medical history;
- A complete physical examination will be performed at certain visits and a limited physical examination will be performed at certain visits. The limited physical examination will consist of measurement of weight; evaluation of lungs, heart, abdomen, and extremities
- Vital signs (including heart rate and blood pressure); serum chemistry, Creatinine clearance (from 24-hour urine), hematology, and urinalysis;
- A urine pregnancy test will be completed at certain visits for women of childbearing potential;
- Glycemic status (HbA_{1c}) will be assessed;

- Adverse events will be recorded and assessed.

7.2 Reporting of Adverse Events

7.2.1 Adverse Events and Serious Adverse Events: definitions, and guidance for reporting:

- An **adverse event (AE)** is any untoward medical occurrence in a patient participating in an investigational trial or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

7.2.1.1 Causality Assessment:

The relationship of an AE to the administration of the study medication is to be assessed according to the following definitions:

No:

Not Related - Onset of the event as relative to administration of the product is not reasonable; or, another cause itself can explain the occurrence of the AE between the administration of study medication and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant medications, therapies, complications, etc.) can be identified of the event.

Unlikely to be related - Onset of the event as relative to administration of the product is possible but another cause itself can explain the occurrence of the event or there are no reasonable grounds for suspecting that the product could have caused the event.

Yes:

Possibly related - Onset of the event as relative to administration of the product is reasonable; however the event could have been due to another equally likely cause

Probably related - Onset of the event as relative to administration of the product is reasonable and is more likely explained by the drug than by any other cause.

Definitely related - Onset of the event as relative to administration of the product is reasonable and there is no other cause to explain the event; or a rechallenge (if feasible) is positive.

- **Serious adverse events (SAE)** are adverse events occurring at any dose which meet one or more of the following **serious criteria**:
  - Results in **death** (i.e. the AE caused or lead to death)
  - Is **life-threatening** (i.e. the AE placed the patient at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)
  - Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
  - Is **disabling** (i.e. the AE resulted in a substantial disruption of the patient's ability to carry out normal life functions)
  - Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a patient exposed to the trial drug prior to conception or during pregnancy)

- It does not meet any of the above serious criteria but **may jeopardize the patient** and **may require medical or surgical intervention** to prevent one of the outcomes listed above

Expected adverse events are those adverse events that are **listed** or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those **not listed** in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

7.2.1.2 Reporting SAE:
If considered a UPIRSTO (a Serious Adverse Events that is possibly due to the study medication) should be reported to the reviewing Institutional Review Board (IRB) according to individual requirements. A copy of that report must be retained at the investigative site and filed in the Investigator Site File.

The Investigator must continue to follow the subject until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies. Within 24 hours of receipt of new information, the investigator must update the SAE form and submit any supporting documentation, (e.g., laboratory test reports, patient discharge summary, or autopsy reports), to the Dr. Fernando Fervenza M.D, Ph.D via email or fax.

Case follow-up with the site will be initiated by Dr. Fernando Fervenza M.D, Ph.D. All site queries will be transmitted by e-mail to an e-mail address containing Dr. Fernando Fervenza M.D, Ph.D or the investigative site's secure e-mail address, or if no secure e-mail address is available, the query will be transmitted by fax.

If a subject is early terminated from the study for a reason other than an SAE, he/she will be followed for 30 days after discontinuation of the study drug. If a subject is terminated early from the study at any time due to an SAE, he/she will be followed until resolution of the SAE or end of study (if SAE is still ongoing).

7.3 Data Safety Monitoring Board:
A four person DSMB (clinical researchers) not affiliated with the study will be responsible for evaluating the progress of the study and will be provided unblinded data on a regular basis to monitor patient safety. This committee will communicate by meeting every 6 months. They will be responsible for determining if and when the study must be discontinued as a result of excessive adverse events. Study data will be provided to the DSMB by the data coordinating center (including all adverse event reports and the GFR data). Data will be reviewed by the DSMB in an unblinded fashion. Randomization codes for each enrolled patient will be provided by the research pharmacist at that specific site. The Committee will make its recommendations

by periodically monitoring progress, data, outcomes, toxicity, safety and other confidential data, and may recommend stopping the clinical trial if an excessive number of serious adverse events are observed.

7.3.1. DSMB-Committee Members

1) Nelson Leung MD, Nephrology and Hypertension, Mayo Clinic Rochester, MN
2) Andrea Kattah MD, MSGME Foundation Dean, Mayo Clinic Rochester, MN
3) Hatem Amer MD, Nephrology and Hypertension, Mayo Clinic Rochester, MN
4) Ziad El-Zoghby MD, Nephrology and Hypertension, Mayo Clinic Rochester, MN

8.0 STATISTICAL CONSIDERATIONS

Sample size

This is an open label phase III study involving 21 patients. The response rate to ACTH in IgAN is unknown. Thus it is impossible to perform a power calculation. At this time a standard t-test will be performed for proteinuria and renal function at Baseline (Day 0), 6month and 12months.

9.0 Data Management and Record Keeping

9.1 Data Management

The data will be housed in both hard copy case report forms (CRFs) and eCRFs through a system called redcap.

9.1.1 Hard Copy CRFs

The hard copy documents will be utilized by the primary site monitor. Each subject will have their own binder which will house each visit CRFs.

9.1.2 Computer Systems

The data will be entered by the local coordinator using a validated computer system conforming to regulatory requirements- redcap. The data should be entered within 5 days of the subject's visit. A; study site personnel must log into the system using their secure username and password in order to enter, review or correct study data. There procedures must comply with the Title 21 Code of Federal Regulations (21 CFR part 11) and other appropriate international regulations. All passwords will be strictly confidential.

9.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other correspondence pertaining to the study must be kept in the appropriate study files at the local site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Mayo Clinic must be notified in writing and be given the opportunity to further store such records.

9.3 Direct Access to source data/documents

Dr. Fernando Fervenza, M.D., Ph.D and the IRB/Independent Ethics Committee, and representatives from the regulatory agencies will have the right, both during and after the clinical study, to review and inspect pertinent medical records related to the clinical trial.

10.0 Quality control and Quality Assurance

The Mayo Clinic will perform quality control and quality assurance checks of all additional sites. Before the enrollment of any subject in this study, designated study personnel will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs. Site visits will be performed by the Mayo Clinic study team. During these visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, safety information will be reviewed for completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Mayo Clinic agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol and accepted standards of Good Clinical Practice.

11.0 Ethics and Good Clinical Practice Compliance

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

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