CLINICAL STUDY PROTOCOL

Protocol Title:	A Multicenter, Comparative Safety and Efficacy Study of ACTHar gel alone or in combination with oral Tacrolimus to reduce urinary proteinuria in patients with idiopathic DNA-JB9 Positive Fibrillary glomerulopathy
Generic Title:	Fibrillary ACTH Tacrolimus Trial (FACT-Trial)
Protocol Number:	NN-002
Phase:	4
Indication:	Reduction of urinary protein excretion & slowing of GFR progression
Sponsor:	NephroNet, Inc. 923 Preserve Bluff Drive Atlanta GA, 30518 Telephone: 770-490-9203
Sponsor Medical Director/Lead PI:	James A. Tumlin, MD
Funding Source:	Mallinckrodt Pharmaceuticals
IND Number:	TBA
IND Holder:	NephroNet Inc
Protocol Version:	3.0, Dated 14March2019

FINAL PROTOCOL APPROVAL SHEET

A Multicenter, Comparative Safety and Efficacy Study of ACTHar gel alone or in combination with oral Tacrolimus to reduce urinary proteinuria in patients with idiopathic DNA-JB9 Positive Fibrillary glomerulopathy

NephroNet, Inc. Approval:

James A. Tumlin, MD
President/CEO
923 Preserve Bluff Drive
Atlanta GA, 30518
Telephone: +1.770-490-9203
Email: jamestumlinmdnephronet@gmail.com

Signature	Date
	19 Dec 2018

SIGNATURE OF INVESTIGATOR

PROTOCOL TITILE: A Multicenter, Comparative Safety and Efficacy Study of ACTHar gel alone or in combination with oral Tacrolimus to reduce urinary proteinuria in patients with idiopathic DNA-JB9 Positive Fibrillary glomerulopathy

PROTOCOL NUMBER: NN-002

VERSION NUMBER: 2.0

VERSION DATE: 14March2019

I agree to conduct this clinical trial according to the protocol described herein, and to comply with its requirements, subject to ethical and safety considerations and guidelines. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and any other institutional requirements.

I understand that the information in this protocol is confidential and should not be disclosed to others without written authorization from Epizon Pharma, Inc., except to the extent necessary to: (1) obtain informed consent from persons to whom the drug may be administered; and (2) inform those directly involved in the execution or the scientific/ethical review of the study.

I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature **Date**

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local clinical research associate (CRA).

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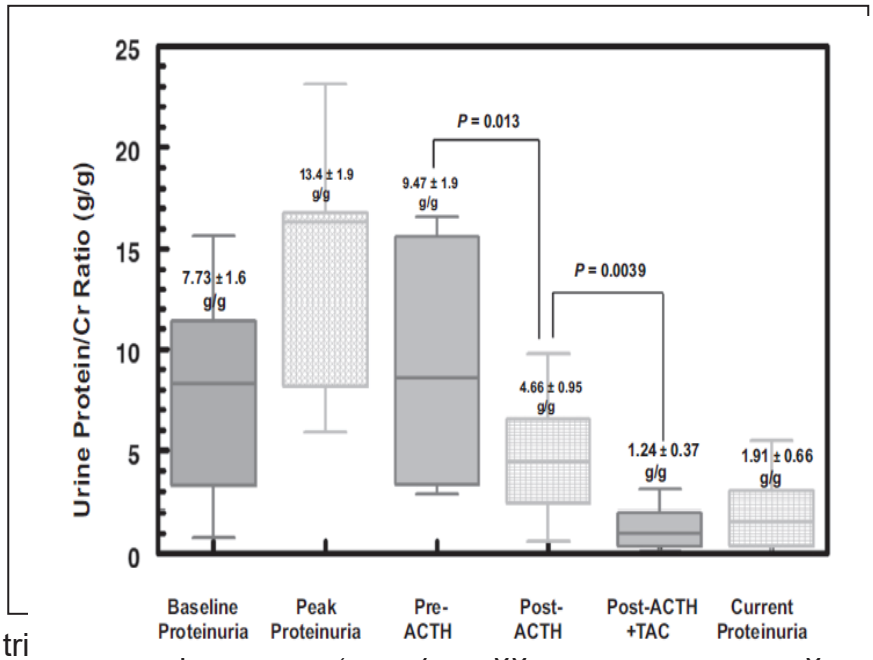
3. LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
BUN	blood urea nitrogen
β-hCG	beta-human chorionic gonadotropin
CBC	complete blood count
CFR	Code of Federal Regulations
CHD	coronary heart disease
CKD	chronic kidney disease
CMP	comprehensive metabolic panel
CRA	clinical research associate
CRO	contract research organization
CVA	cerebrovascular accident
DNA	deoxyribonucleic acid
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDC	electronic data capture
EOS	End-of-Study (visit)
EOT	End-of-Treatment (visit)
ESRD	end-stage renal disease

FDA	Food and Drug Administration
FSI	first subject in
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IND	Investigational New Drug application
INR	International Normalized Ratio
IOM	Institute of Medicine
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NADP	nicotinamide adenine dinucleotide phosphate
NOAEL	no-observed-adverse-effect-level
PCR	polymerase chain reaction
PT	Pro thrombin Time
PTT	partial thromboplastin time
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation

SMF	Site Master File
SOC	System Organ Class
SRC	Safety Review Committee
TIA	transient ischemic attack
U-VEGF121	Urinary Vascular Endothelial Growth Factors Isoform 121
Urinary VEGF-165	Urinary Vascular Endothelial Growth Factors Isoform 165
Urinary VEGF-189	Urinary Vascular Endothelial Growth Factors Isoform 189
Urinary VEGF-206	Urinary Vascular Endothelial Growth Factors Isoform 189
Urinary MCP-1	Monocyte chemoattractant protein 1,
Urinary Synaptopodin	Urinary Synaptopodin
Urinary TGF-beta	Urinary Transforming Growth Factor Beta
Urinary Podocalyxin	Urinary Podocalyxin
Urinary Nephrin	Urinary Nephrin
WBC	white blood cell
WHO	World Health Organization

Study Title	A Multicenter, Comparative Safety and Efficacy Study of ACTHar gel alone or in combination with oral Tacrolimus to reduce urinary proteinuria in patients with idiopathic DNA-JB9 Positive Fibrillary Glomerulopathy
Study Number	NN-002
Clinical Phase	Phase 4
Indication	Reduction of urinary protein excretion & slowing of GFR progression
Projected Number Enrolled Patients:	34
Projected Number NephroNet Sites:	7-10
Background	Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease that is characterized by glomerular accumulations of nonbranching, randomly arranged fibrils. The most common histologic presentation is mesangial proliferative with areas of sclerosis. It is unknown whether specific histologic patterns have a better or worse prognosis. The deposition of fibrils can be found in the mesangium, basement membranes of glomerular endothelial cells and within the sub-epithelial space. Fibrillary proteins differ from amyloid both in diameter, arrangement the and lack of Congo red staining. A recent review of all renal biopsies Arkana Laboratories between 2014-2015 demonstrated that 105 patients were diagnosed with Fibrillary GN (unpublished data). The mean age of these patients was 60 years old with a mean eGFR of 45 mls/min and UP/Cr ratio of 5.380 grams. The majority of these patients had been previously treated with 2 or more different immunosuppressive agents with little to no success. There are currently no approved or generally accepted therapies for Fibrillary GN. Previous studies have shown that up to 70% of patients progress to ESRD within 4years[9]. Rituximab has been studied in two previous trials with an approximate response rate of 20%. A recent study treated 15 patients with refractory Fibrillary GN for an average of 6 months with ACTHar gel and achieved a complete or partial remission 59% of patients. Among the 7 ACTHar responsive patients, the UP/Cr ratio dropped by 75% from a mean of

Background	5435 to 1335 mg/gm. The efficacy of combination therapy with ACTHar and Tacrolimus was recently shown in a study of 22 patients with idiopathic Membranous GN (9) or FSGS (13). After 6 months of ACTHar gel therapy alone, 59% of patients achieved a complete or partial remission. When oral Tacrolimus was added to existing ACTHar gel, complete and partial response rates increased significantly to over 90%. As shown in figure-1, the addition of tacrolimus to patients exhibiting a partial response to ACTH resulted in a further reduction in UP/Cr. While the number of patients in these  tri calcineurin inhibitor with a melanocortin receptor agonists could reduce proteinuria and stabilize renal function. The NephroNet clinical trial consortium is proposing a multicenter study investigating the safety and efficacy of ACTHar gel alone or combination with oral Tacrolimus in patients with Fibrillary glomerulopathy.
Study Design	This is a multicenter, Phase 4, prospective, open labeled study to compare the safety, tolerability, and efficacy of a 12-month course of ACTHar Gel alone or in combination with oral Tacrolimus to reduce UP/Cr ratio in patients with DNA-JB9 positive Fibrillary Glomerulopathy.

Hypothesis and Specific Aims	**Hypothesis#1:** A 12-month treatment with combination ACTHar gel and Tacrolimus therapy will be superior to ACTHar gel therapy alone in lowering urinary protein to creatinine (UP/Cr) ratios in patients with idiopathic DNA-JB9 positive Fibrillary GN **Specific Aim #1**-will randomize 35 patients with biopsy proven DNA-JB9 positive Fibrillary glomerulopathy to receive a 12-month course of ACTHar gel at 80 units SQ 2X/week alone or in combination with oral Tacrolimus at 1.0 mg BID (targeting for trough Tacrolimus dose of 4-6 ng/ml). **Hypothesis#2:** Treatment with combination ACTHar gel and Tacrolimus therapy will result in a higher eGFR after 24 months of follow up than patients randomized to ACTHar gel therapy alone **Specific Aim #2**-will determine the change in eGFR from baseline to 24 months of follow for patients with biopsy proven DNA-JB9 positive Fibrillary glomerulopathy. It is anticipated that at 24 months (12 months after completing therapy) patients randomized to ACTHar gel plus Tacrolimus will have higher eGFR compared to patients receiving ACTHar gel alone. **Hypothesis #3:** Combination therapy of ACTHar Gel and Tacrolimus in patients with DNA-JB9 positive Fibrillary Glomerulopathy will lead to significantly lower urinary markers of podocyte injury compared to patients receiving ACTHar gel therapy alone. **Specific Aim #3**-will compare the relative changes in the following urinary biomarkers will be performed: 1. Urinary VEGF 121, VEGF-165 2. Urinary VEGF-189, VEGF-206 3. Urinary MCP-1 4. Urinary Synaptopodin 5. Urinary TGF-beta 6. Urinary Podocalyxin 7. Urinary Nephrin Levels will be measured at baseline prior to treatment and after 12 months of ACTHar ge therapyl alone or in combination with oral Tacrolimus. The relative reduction urinary biomarkers will also be compared between the two treatment groups.

Study Population	A total of **34** patients will be enrolled. Group 1 (17 patients) ACTHar gel 80 units 2X/week alone for 12 months of therapy. Group 2 (17 patients) ACTHar get 80 units 2X/week plus oral Tacrolimus 1.0 mg BID titrated to trough Tacrolimus levels between 4-6 ng/ml Anticipated drop out rate 10%.
Inclusion Criteria	**Histologic Inclusion Criteria** Histologic Criteria: All patients with a diagnosis of The Fibrillary GN will be classified according to the Nasr nomenclature: 1) Renal biopsy demonstrating DNA-JB9 Positive staining within 3 years of study randomization 2) Mesangial expansion with/without glomerular sclerosis 3) Membranous changes with or without diffuse sclerosis 4) Crescents or endocapillary proliferation 5) Level of interstitial fibrosis **Note:** Patients with > 50% interstitial fibrosis will not be eligible for study participation **Note:** Patients with monoclonal staining of fibrillary fibers will not be eligible for study participation **Inclusion Criteria:** 1) Male/Female age ≥ 18 2) Biopsy proven Fibrillary GN within 3 years of study randomization 3) Stable Maximum RAAS inhibition X 4 weeks prior to randomization **Note: Maximum RAAS inhibition will be left to the discretion of the site PI** 4) eGFR > 25 mls/min calculate by the CKD-EPI formula 5) UP/Cr ratio ≥ **2000 mg/gm**

	5) Note: IF UP/Cr less than **2000 mg/gm**, a formal 24-hour urine collection for total protein can be performed. The total 24-hour protein will need to **>/= 2000mg**. 6) Blood pressure targeted to ≤ 140/90 at the time of randomization 7) Patients with MGUS without history of myeloma WILL be eligible. 8) Patients with monoclonal staining for fibrillary fibers will be excluded 9) Patients with Type II non-insulin dependent diabetes WILL be eligible provided the renal biopsy does not show nodular Kimmelstiel Wilson lesions
Exclusion Criteria	**Exclusion Criteria;** 1) Patients with MGUS and history of myeloma WILL NOT be eligible 2) Patients with active viral production of either hepatitis B or C as evidence by historical PCR test positive for active viral shedding 3) HIV seropositivity 4) Renal biopsy data with > 50% Interstitial Fibrosis 5) Patient with active or a known history lymphoma 6) Patients with insulin Dependent diabetes mellitus will be excluded **Note: patients with Type II diabetes mellitus that are well controlled WITHOUT the need for insulin WILL be eligible for the study.** 7) Patients with Type II non-insulin dependent diabetes WILL be eligible provided the renal biopsy does not show nodular Kimmelstiel Wilson lesions. 8) Patients receiving steroids, MMF, cyclophosphamide, Azathioprine or other immunosuppressive agent with 4 weeks of study randomization Note: Washout of these medications will be allowed at the screening visit 9) Patients having received Rituximab or B cell modifying biologic therapy within 6 months of randomization

Primary Endpoint:	**Primary Endpoint:** The change in UP/Cr ratio in patients with biopsy proven Fibrillary GN after 12 months of treatment with treated with ACTHar gel (80 units SQ 2X/week) alone **OR** in combination with oral Tacrolimus (1.0 mg PO BID). The change in UP/Cr for each group will also be compared to baseline UP/Cr ratios prior to randomization
Secondary Endpoint	**Secondary Endpoints:** 1) The relative change in UP/Cr at 24 months (12 months after stopping both ACTH and Tacrolimus) in the ACTHar gel group and the ACTHar gel + Tacrolimus group. 2) The percentage of patients in the ACTHar gel alone versus ACTHar gel + Tacrolimus group that achieves complete, partial or clinical responses after 12 months of therapy 3) The change in eGFR (measured by CKD-EPI formula) between the ACTHar gel and ACTHar Gel + Tacrolimus groups after 24 months of treatment with ACTHar gel alone or in combination with oral Tacrolimus. In addition, we will also compare the relative change in eGFR between those patients receiving ACTHar gel alone with those randomized to combination therapy. 4) To compare the change in urinary biomarkers (see below) at baseline and after 12 months of treatment with ACTHar gel alone or in combination with Tacrolimus. The patients urinary biomarker levels after 12 months of therapy will be compared between the ACTHar gel alone group and ACTHar gel + Tacrolimus group. a) Urinary VEGF 121, 165 189, and206 b) Urinary MCP-1 c) Urinary Synaptopodin d) Urinary TGF-beta e) Urinary Podocalyxin f) Urinary Nephrin **Fibrillary GN patients with concurrent Type II diabetes mellitus:** To determine whether ACTHar gel therapy resulted in

Pre-Defined Sub-Groups for Post-Hoc Analysis:	hyperglycemia in patients with concurrent Diabetes and whether that led to early termination from the study. We will also determine whether the presence of diabetes led to increased proteinuria over time, led to more rapid decline in renal function and altered the response to immunosuppressive therapy. **Fibrillary Patients with Low Urinary Levels of VEGF 121, 165, 189, 206** To determine whether ACTH alone or in combination with Tacrolimus can restore production of urinary VEGF. The level of urinary VEGF will also be corrected with the level of GFR and the number of senescent glomeruli and degree of interstitial fibrosis on the primary biopsy. **Fibrillary GN Patients with the presence of Cellular Crescents** To determine whether this specific histologic finding correlated with increased or reduced responsiveness to ACTHar gel alone or in combination with Tacrolimus
Study Schedule	**Year 1:** Study recruitment of 34 patients with biopsy proven DNA-JB9 positive Fibrillary Glomerulopathy Each patient will undergo 12 months of treatment with 17 patients randomized to ACTHar gel alone (17 patients) or to ACTHar gel plus oral Tacrolimus (17 patients) **Year 2:** Follow up and observation for 12 months OFF ACTHar gel or ACTHar gel and Tacrolimus
Duration of Study	The expected duration study participation for each patient will be two (2) years. One year of ACTHar gel treatment alone or in combination with Tacrolimus and then one year for follow up off drug treatment.
Trial Endpoint Definitions:	1) Complete remission: < 300 mg UP/Cr mg/gm 2) Partial Remission: > 50% reduction in UP/Cr from baseline values

	3) Clinical Response: >30%-<50% in UP/Cr from baseline values
Patient Identification & Recruitment	**Patient Identification & Recruitment:** Two major Renal pathology centers will be involved in the recruitment of newly diagnosed patients with Fibrillary glomerulopathy: 1) Arkana Laboratories and 2) Columbia University. New or repeat renal biopsies determined by Arkana Laboratories to be consistent with Fibrillary GN will be identified by the attending pathologist and referred to a clinical research coordinator affiliated with the Arkana Clinical Research Division. During the standard of care verbal review of the biopsy result, the attending pathologist will inquire whether the referring nephrologist would like to know more about the FACT Trial including his/her patients eligibility to participate in the study. If the referring Nephrologist expresses a desire to know more about the study, he/she will be given the option of being contacted by a member of the NephroNet study team.
Patient Pre-Screening and HIPPA Release	Once the primary nephrologist has communicated with a potential study patient and determined that he/she is interested in participating in the trial, the primary Attending will forward an IRB approved HIPPA release to the patient. After signing the HIPPA release, the potential study patients medical records will then be sent to the National PI AND the local site PI for screening and eligibility. If it is determined that the patient meets eligibility requirements, the patient will be provided transportation and lodging to the nearest FACT Trial site. The potential patient's medical records will be reviewed by the National and Local PIs. If it is determined that the patient is a candidate, he/she will be and the FACT team has occurred, a preliminary review of the protocol and its objectives will be made with the attending physician. The attending physician will either contact the prospective patient directly or seek permission from the patient to be contacted by the FACT team. Patients expressing a desire to know more about the study will be contacted by Dr. Tumlin the Medical Director/Lead PI and the Site PI nearest to the patient's location.
Patient Consenting	Patients completing an initial screening assessment and who meet the clinical inclusion/exclusion criteria will be sent a copy of the study IRB approved Consent. A telephone

	conference call with the prospective patient will be arranged to discuss in details of the study; the risks/benefits of the study drug, as well as details regarding patient requirements and travel to and from the study site. The patient will be given time to review the consent with their families and other physicians. If is determined by the Medical Director and the FACT Site PI that the patient is a likely candidate for the study, a travel agent will contact patient and make arrangements for airfare and overnight accommodations to visit the FACT PI. Both the airfare and overnight accommodations will be provided by NephroNet. If a patient lives within approximately **4 hours** of the FACT site, they will be reimbursed for mileage and hotel. There will be a total of 13 visits per patient per site. Patients agreeing to participate in the FACT sign consent at their first screening visit.
Number of total Clinic Visits	Thirteen (13) visits for total study: Pre-screening visits- two (2) Study Drug Treatment visits- six (6) Post Study Drug Treatment visits- five (5)
FACT-Trial: Study Design	**Study Design:** This study will be a multi-center, prospective, randomized, **open-labeled** intervention trial of **34 patients** randomized to 52 weeks of ACTHar gel alone or ACTHar gel plus oral Tacrolimus. **Drug Dosing:** **Group-1:** ACTHar gel alone-patients will be receive 80 units SQ Q 2X/week for 52 weeks **Group-2:** ACTH gel 80 units 2X per week plus oral Tacrolimus (1.0 mg BID) titrating to a trough level of 4-6 ng/ml for 52 weeks **Note:** Patient with type II diabetes will be allowed to dose at **24 units/day** (0.3 mls SQ Q day) to reduce glucose fluctuations and simplify management of diabetes at the discretion of the PI. **Protocol-Schedule and Follow Up: Clinic Visits:**

- **Visit 1: Pre-Randomization Screening & Consenting Visit:** Patients that have gone through the Pre-screening review and considered to be eligible for study participation will seen by the local site PI for formal consenting two months prior to study randomization. The patient will then be see the FACT trial site PI who will perform a complete physical exam and obtain routine laboratory testing including a urine to protein Cr ratio.

  Pre-Randomization Screening & Consenting Visit (V1): Blood and Urine Study Samples: Blood samples (5 mls) for serum and plasma will be obtained at each visit. Blood samples will be centrifuged at 3000 RPM for 5 minutes and 250 ul of plasma or serum will be transferred to an O-ring sealed cryovials and frozen at -80^{o}C until analyzed. Each 10-ml sample of urine will be added to 100 ul of Thermo Scientific HALT proteinase inhibitor solution and then centrifuged at 3,000 rpm for 10 minutes at 4°C. Then, 250 µL of the urine supernatant will be transferred to an O-ring sealed cryovials and frozen at -80^{o}C until analyzed.

- **Visit 2: Pre-Randomization Screening #2) "Optimization & Run-In Phase":** After the initial pre-screening visit, the prospective patients will enter a 4-week "optimization and run-in phase" during which patients will have their blood pressure optimized to a "pre-randomization" target level of 140/90. During the "run-in phase", RAAS blockers will not be modified and target blood pressure will be achieved using antihypertensive agents that do not alter urinary protein excretion (e.g. Nifedipine Hydralazine).

- **Visit 3: Randomization/Baseline:** After the 4-week run-in phase, patient will be flown back to the FACT trial site where they will undergo formal randomization. When the site PI determines that the patient has met all inclusion and exclusion criteria, they contact Dr. Tumlin and the NephroNet data coordinating center for randomization. Each patient will then undergo a physical exam and routine blood and urine laboratory studies. The UP/Cr from the pre-

screening and randomization visits will be averaged and this value will be considered the "baseline UP/Cr" for that patient.

Note: If the pre-screen and randomization UP/Cr values differ by more than 50%, the patient will be allowed to collect a third UP/Cr ratio one week later. The average of those 3 UP/Cr ratios will be recorded as the patient's baseline proteinuria.

Baseline- Blood and Urine Study Samples: Blood samples (5 mls) for serum and plasma will be obtained at each visit. Blood samples will be centrifuged at 3000 RPM for 5 minutes and 250 ul of plasma or serum will be transferred to an O-ring sealed cryovials and frozen at -80^{o}C until analyzed. A 10-ml sample of urine will be centrifuged at 3,000 rpm for 10 minutes at 4°C. Then, 250 µL of the supernatant will be transferred to an O-ring sealed cryovials and frozen at -80^{o}C until analyzed

- **Visit 4: 14 Days Post Randomization Visit:** 14 Days Post Randomization (Visit 4) will be optional for patients traveling from long distances. Would request that patient visit nephrologist in home town if any adverse events of concern are reported.

- **Visits 5 – 7: Study Visits-Months 3 (V5), 6(V6) & 9(V7) :** We will be conducted in like manner to Randomization visit. Each patient will get a complete physical exam. Standard blood and urine studies will be performed as well as plasma, serum and urine study sample collections. Tacrolimus Trough Levels will be drawn for those patients randomized to the Tacrolimus arm.

- **Visit 8: Month 12: Primary Endpoint Evaluation**: All patients completing of 52 weeks of ACTHar gel therapy alone or in combination with Tacrolimus will be examined for their change in UP/Cr as compared to their baseline levels of urinary protein. Patients will be asked to bring 2 first morning voids of urine. These two samples will be averaged and used for

	determination of the percentage of patients achieving the primary endpoint. **Complete Responders: < 300 mg/gm UP/Cr ratio** Patients that have reached this milestone will be weaned off ACTHar Gel with or without Tacrolimus over the subsequent 14 days. Sites will start the ACTHar Gel wean at 40 units and reduce over a 2 week taper period at the discretion of the principal investigator of each site. **Non-or Partial Responders: > 50% Reduction in UP/Cr ratio to minimum value of 2000 mg/gm:** Patients will follow the same weaning protocol as the complete responders described above. • **Visit 9: ACTHar Washout Visit:** 14 Days Post End of Treatment (Visit 9) will be optional for patients traveling from long distances and will occur after the post treatment taper. The Study Staff will request that the patient visit a Nephrologist in the patient's home town if any adverse events of concern are reported. • **Visits 10 -12: Follow-Up Visits-Months 15 (V10), 18(V11) & 9(V12):** We will be conducted in like manner to Randomization visit. Each patient will be get a complete physical exam. Standard blood and urine studies will be performed as well as plasma, serum and urine study sample collections. • **Visit 13: Month 24 Visit: Secondary Endpoint Evaluation:** Patients completing 104 weeks of study participation will be evaluated for the following: 1) Percentage of Complete Responder patients weaned off ACTHar gel and Tacrolimus that developed a relapse after 12 months of no therapy. 2) Percentage of patients in the ACTHar gel alone group that demonstrated additional reduction in UP/Cr

	ratio following the addition of Tacrolimus at Week 52. **Hyperkalemia:** Patient developing hyperkalemia defined as > 5.5 meq/L will undergo the following interventions: Intervention #1: Review dietary sources of potassium and assess patient compliance with prescribed dietary restrictions. Intervention #2: Adding or increasing dose of a loop diuretic. If they patient was already taking a diuretic as part of their standard of care regimen, the dose or frequency will be increased according to the discretion of the Site PI. Intervention #3: For patients with continued hyperkalemia following intervention 1 & 2, the Site PI can consider adding a Thiazide diuretic (HCTZ or Metolazone) to the current loop diuretic. Intervention #4: For patients with continued hyperkalemia following intervention 1 & 2 & 3, the dose of Tacrolimus can be reduced to 0.5 mg BID. Combining Thiazide and Loop diuretic therapy to AM-PM doses Intervention #5: For patients with continued hyperkalemia following intervention 1 & 2, 3, & 4, the patient can discontinued from Tacrolimus. Note: Any Site PI that chooses to treat a study patient's hyperkalemia with Patiromer may do and keep the patient in the study. Any decision to use Patiromer is solely at the discretion of the Site PI. **Hyperglycemia:** Patients developing intractable hyperglycemia defined as > 400 mg/dl can have their current diabetic medications modified. For patients with continued hyperglycemia despite increases in diabetic therapy, the dose of ACTHar gel can be reduced by 50%. Patients with persistent hyperglycemia can be withdrawn from the study at the discretion of the Site PI. Note: Any Site PI choosing to use of Insulin to treat a study patient's hyperglycemia can do and keep the patient in the

study. Any decision to use institute Insulin therapy is solely at the discretion of the Site PI.

Lower Extremity Edema: Patients developing increasing lower extremity edema can have their diuretic regimen increased by either dose or frequency. Patients continuing to have edema with maximal Loop diuretics can be treated with dual Loop and Thiazide diuretic therapy. All decisions as the management of lower extremity edema will be left to the discretion of the Site PI.

Statistical Analysis Sample Size and Power.

The sample size was calculated to detect a 40% difference in the mean UP/Cr ratio after 12 -month of ACTHar gel therapy alone or with oral Tacrolimus. Analysis will be intention to treat for all patient receiving at least one week of drug therapy. Based on the estimated variability of 30% for the change in UP/Cr ratio (CV) a sample size of 17 patients per arm (total-34) will be needed to provide 80% power to see a difference with a P value of < 0.05. A Fisher exact test will be applied for comparisons of adverse event frequencies. All tests were two-tailed with a *P* value-0.05 considered significant.

References:

1) Laser Microdissection and Proteomic Analysis of Amyloidosis, Cryoglobulinemic GN, Fibrillary GN, and Immunotactoid Glomerulopathy Sanjeev Sethi,* Jason D. Theis,* Julie A. Vrana,* Fernando C. Fervenza,† Anjali Sethi,‡ Qi Qian,† Patrick Quint,* Nelson Leung,* Ahmet Dogan,* and Samih H. Nasr* Clin J Am Soc Nephrol 8: 915–921, 2013.

2) Fibrillary Glomerulonephritis: A Report of 66 Cases from a Single Institution *Samih H. Nasr,* Anthony M. Valeri,† Lynn D. Cornell,* Mary E. Fidler,* Sanjeev Sethi,* Nelson Leung,‡ and Fernando C. Fervenza‡ Clin J Am Soc Nephrol* 6: 775–784, 2011.

3) Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy Charles E. Alpers and Jolanta Kowalewska. *J Am Soc Nephrol* 19: 34–37, 2008.

4) Plasmapheresis leading to remission of refractory

nephrotic syndrome due to fibrillary glomerulonephritis: a case report Rainer U Pliquett1*, Peter Mohr1, Badr El Din Mukhtar2, Matthias Girndt1 and Silke Markau1 Journal of Medical Case Reports 2012, 6:116

5) Rituximab treatment for fibrillary glomerulonephritis Jonathan Hogan, Michaela Restivo, Pietro A. Canetta, Leal C. Herlitz, Jai Radhakrishnan, Gerald B. Appel and Andrew S. Bomback Nephrol Dial Transplant (2014) 0: 1–7

6) Rituximab Treatment of Fibrillary Glomerulonephritis *Michael Collins, DO,1 Sankar D. Navaneethan, MD,2 Miriam Chung, MD,3 James Sloand, MD,2 Bruce Goldman, MD,2 Gerald Appel, MD,3 and Brad H. Rovin, MD1 Am J Kidney Dis* 52:1158-1162, *2008*

7) The Occurrence or Fibrillary Glomerulonephritis in Patients with Diabetes Mellitus May Not Be Coincidental: A Report of Four Cases Fayna González-Cabrera,1 Fernando Henríquez-Palop,1 Ana Ramírez-Puga,2 Raquel Santana-Estupiñán,1 Celia Plaza-Toledano,1 Gloria Antón-Pérez,1 Silvia Marrero-Robayna,1 Davinia Ramírez-Medina,1 Roberto Gallego-Samper,1 Nicanor Vega-Díaz,1 Rafael Camacho-Galan,3 and José C. Rodríguez-Pérez1 Case Reports in Medicine Volume 2013, Article ID 935172.

8) J. A. Tumlin,[1,2] C. M. Galphin,[2] and B. H. Rovin[3] Advanced Diabetic Nephropathy with Nephrotic Range Proteinuria: A Pilot Study of the Long-Term Efficacy of Subcutaneous ACTH Gel on Proteinuria, Progression of CKD, and Urinary Levels of VEGF and MCP-1. Journal of Diabetes Research Article ID 489869, 8 pages, 2013

9) Stephen M. Korbet,* Melvin M. Schwartz,† and Edmund J. Lewis* Immuotactoid Glomerulopathy (Fibrillary Glomerulonephritis) Clin J Am Soc Nephrol 1: 1351–1356, 2006

Cycle (Days or Months)	Pre-Screen	Pre-Screen_Randomization (V1 & V2)		V3_Randomization & Baseline	Visit 4	Study Visit 5, 6, & 7	EOT- V8	Optional- V9	F/U- V10, 11 & 12	Visit 13- End of Study
		-2 Months	-1 Month	Baseline	(14 Days Post Rand **3)	3, 6 & 9 Months	12 Months	2 Weeks Post EOT**4 (54 Weeks)	15, 18 & 21 Months	24 Months
Window (weeks)		+/- 2 Wks	+/- 2 Wks	+/- 2 Wks	+/- 1 Wk	+/- 2 Wks	+/- 2 Wks	+/- 1 Wk	+/- 2 Wks	+/- 2 Wks
HIPPA Release	X**1									
Informed Consent		X								
Full H&P		X		X			X			X
Limited H&P			X		X	X		X	X	
Blood		X	X	X	X	X	X	X	X	X
Pressure										
Study Drug Administration				X		X				
Stable		X	X	X	X	X	X	X	X	X
ACE or ARB										
AE/SAE Events				X	X	X	X	X	X	X
Laboratory Assessments										
CBC		X	X	X		X	X		X	X
CMP		X	X	X		X	X		X	X
UA		X	X	X		X	X		X	X
UP/Cr		X	X	X		X	X		X	X
HgbA1c **2						X	X		X	X
Tracrolimus										
Trough Levels (if in Tacrolimus Group)						X	X			
Exploratory Laboratory Assessments										
Urinary		X	X	X		X	X		X	X
VEGF										
Urinary		X	X	X		X	X		X	X
MCP-1										
Urinary		X	X	X		X	X		X	X
TGF-beta										
Urinary		X	X	X		X	X		X	X
Synapto										
Urinary		X	X	X		X	X		X	X
Future Proteins										

**1: National PI & Local PI to review patient records for study eligibility prior to Pre-Randomization Visit 1

**2: HgbA1c will be optional for diabetic patients left to discretion of the site PI

**3: 14 Days Post Randomization (Visit 4) will be optional for patients traveling from long distances. Would request that patient visit nephrologist in home town if any adverse events of concern are reported.

**4: 14 Days Post End of Treatment (Visit 9) will be optional for patients traveling from long distances. Would request that patient visit nephrologist in home town if any adverse events of concern are reported.