NCT03656692

CLINICAL STUDY PROTOCOL

A Multicenter, Open Label Pilot Study to Explore the Efficacy and Safety of Acthar® in Subjects With Severe Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

Protocol Number: MNK61074105

Date of Amendment 3:	18 September 2019
Date of Amendment 2:	15 April 2019
Date of Amendment 1:	26 July 2018
Date of Original Protocol:	05 June 2018

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6. SYNOPSIS

<table>
<tr><td colspan="2">Study Title: A Multicenter, Open Label Pilot Study to Explore the Efficacy and Safety of Acthar® in Subjects With Severe Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis</td></tr>
<tr><td>Protocol MNK61074105</td><td>Type: Phase 4</td></tr>
<tr><td>Condition/Disease:</td><td>Severe Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis (NIPPU)</td></tr>
<tr><td>Approximate Number of Subjects: 30</td><td>Approximate Duration of Subject Participation: 48 weeks</td></tr>
<tr><td>Approximate Study Centers: 10 in the US</td><td>Approximate Duration of Study: 18 months</td></tr>
<tr><td colspan="2">Design:
This is a multicenter, multiple dose, open label study to examine the effects of Acthar in adult subjects with severe NIPPU. Approximately 30 subjects will be enrolled. Subjects with current severe NIPPU who meet entry criteria will be treated with Acthar 1 mL (80 units [U]) subcutaneously (SC) 2x/week for 36 weeks. Followed by a taper to Acthar 1 mL (80 U) SC once a week for 2 weeks, then 0.5 mL (40 U) SC once a week for 2 weeks.
All subjects will have a follow-up contact 28 (± 14) days after their last dose of study drug.</td></tr>
<tr><td colspan="2">Objectives:</td></tr>
<tr><td>Primary Objective</td><td>Endpoints</td></tr>
<tr><td>To explore the efficacy of Acthar in subjects with severe NIPPU in reducing aqueous and vitreous indicators of inflammation.</td><td>Proportion of subjects with a 2 or more step reduction from baseline (or achievement of Grade 0) in vitreous haze at 36 weeks.
Proportion of subjects with a 2 or more step reduction from baseline (or achievement of Grade 0) in aqueous flare at 36 weeks.
Proportion of subjects with a 2 or more step reduction from baseline (or achievement of Grade 0) in aqueous cells at 36 weeks.</td></tr>
<tr><td>Secondary Objective</td><td>Secondary Endpoints</td></tr>
<tr><td>To further explore the safety and tolerability of Acthar in subjects with severe NIPPU.</td><td>Incidence and severity of ocular adverse events (AEs).
Incidence and severity of other AEs.
New or worsening cataracts.
Mean change in intra-ocular pressure (IOP).</td></tr>
<tr><td>Exploratory Objectives</td><td>Exploratory Endpoints</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Entry Criteria:

Male or nonpregnant, nonlactating female subjects 18 years of age or older with who have been diagnosed with current severe NIPPU and have active disease at the Baseline Visit as defined by the presence of at least 1 of the following parameters in at least one eye despite at least 2 weeks of maintenance therapy with oral prednisone (or oral corticosteroid equivalent):

Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion.

≥ 2+ anterior chamber cells (Standardization of Uveitis Nomenclature [SUN] criteria).

≥ 1.5+ vitreous haze.

Subjects must be willing to taper their current doses of corticosteroid and immunomodulatory therapy to the minimum effective dose during the study.

Subjects may be under treatment with any immunosuppressants, immunomodulators, or biologic agents for a comorbid condition as long as they are on a stable dose for 2 weeks prior to screening. Subjects with proliferative or severe nonproliferative diabetic retinopathy, clinically significant macular edema due to diabetic retinopathy, neovascular/wet age-related macular degeneration, abnormality of vitreo-retinal interface with the potential for macular structural damage independent of the inflammatory process or severe vitreous haze that precludes visualization of the fundus at the Baseline Visit will be excluded.

Subjects with Type 1 or Type 2 diabetes mellitus, tuberculosis, history of hepatitis, peptic ulcer, active infection, or any contraindication for Acthar will be excluded.

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Concomitant Medications and Treatments:

Subjects are not permitted to receive live or live-attenuated vaccines; topical, ophthalmic, or intra-ocular corticosteroids for a concomitant condition during the study.

The use of corticosteroid therapy and immunomodulators for uveitis are permitted provided the subject has been on a stable dose for at least 2 weeks prior to the Screening Visit and is willing to taper to the lowest effective dose during the study.

Subjects with stable comorbid conditions that are commonly associated with uveitis may continue with their current therapies that were stable for 2 weeks prior to screening.

All medications and nondrug therapies (eg, blood transfusions, oxygen supplementation) taken from 30 days prior to the Screening Visit and throughout the study will be recorded.

Study Drug and Treatment Administration:

Acthar is a sterile preparation of adrenocorticotropic hormone (ACTH) analogue formulated in a gel for repository administration. Acthar is supplied as 5 mL multidose vials. Acthar vials contain 80 U of ACTH per mL.

The following treatments will be administered to all subjects:

Acthar 1 mL (80 U) SC doses 2x/week for 36 weeks, followed by a taper to 1 mL (80 U) SC doses once per week for 2 weeks and then 0.5 mL (40 U) SC once a week for an additional 2 weeks.

Efficacy Evaluations:

The following efficacy assessments will be evaluated: Ophthalmic Examination, Spectral domain optical coherence tomography (SD-OCT), Fundus Photography, Fluorescein Angiography, and T-cell numbers.

Safety Evaluations:

The following safety assessments will be evaluated: adverse events, ophthalmology examinations, physical examination, clinical laboratory test results (Chemistry, Hematology, lipid profile and Urinalysis), glycosylated hemoglobin (HbA1c), pregnancy testing, and vital signs.

Quality of Life/ Health Outcome Evaluations:

The following quality of life (QOL)/health outcome assessments will be evaluated: National Eye Institute Visual Function Questionaire-25.

Statistical Methods:

Analysis Populations

The Modified Intent-to-Treat (mITT) Population will include all subjects who receive at least 1 dose of study drug and who contribute any postbaseline efficacy data to the study.

The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol, have no missing primary endpoint data, and do not have any major protocol deviations.

The Safety Population will include all subjects who receive 1 or more doses of study drug.

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Sample Size A total of 30 subjects will be enrolled in this study. No formal sample size calculations were performed. The sample size was determined empirically.

Efficacy Analysis

All efficacy analyses will be performed on the mITT population. Selected analyses will be performed on the Per-Protocol population.

The primary efficacy endpoints will include:

Proportion of subjects with a 2 or more step reduction from baseline (or achievement of Grade 0) in vitreous haze at 36 weeks.

Proportion of subjects with a 2 or more step reduction from baseline (or achievement of Grade 0) in aqueous flare at 36 weeks.

Proportion of subjects with a 2 or more step reduction from baseline (or achievement of Grade 0) in aqueous cells at 36 weeks.

The primary efficacy endpoints will be analyzed on both mITT population and the Per-Protocol population. The endpoints will be summarized with frequency tables and evaluated with one-sample binomial test. The nominal p-values along with the 95% confidence intervals (CI) will be provided.

For subjects with both eyes affected, the change from baseline will be determined based on the eye with the worst severity at baseline. If both eyes have the same severity at baseline, the right eye will be used to determine change from baseline. The same principle will be applied to efficacy endpoints when change from baseline is evaluated.

Other efficacy endpoints will be summarized with descriptive statistics and the changes from baseline will be evaluated with test statistics and/or 95% CI as appropriate.

Safety Analysis

Treatment-emergent adverse events and serious adverse events will be summarized using the appropriate version of MedDRA by preferred term within system organ class.

Other safety data will be listed and summarized descriptively or graphically, as appropriate.