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AWARD NUMBER: W81XWH-12-2-0136

TITLE: Phase 2 Clinical Trial of AC105 (Mg/PEG) for Treatment of Acute Spinal Cord Injury (SCI)

PRINCIPAL INVESTIGATOR: Andrew Blight, PhD

RECIPIENT: Acorda Therapeutics, Inc.
Ardsley, NY 10502

REPORT DATE: October 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
Octoeber 2013	Annual Report	30 September 2012-29 September 2013

4. TITLE AND SUBTITLE

Phase 2 Clinical Trial of AC105 (Mg/PEG) for Treatment of Acute Spinal Cord Injury (SCI)

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-2-0136

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Adrew Blight, PhD

E-Mail: ablight@acorda.com

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Acorda Therapeutics, Inc.

Ardsley, NY 10502

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Acorda Therapeutics, Inc. is developing the polymer formulation of magnesium, known as AC-105, for the treatment of acute spinal cord injury. This trial is partially supported by the funds from this Department of Defense Broad Agency Announcement for Extramural Medical Research grant. The primary hypothesis of this proposed study is that treatment of people with acute SCI with AC-105 will result in greater normalization of CNS Mg than treatment with MgCl2 or saline solutions and potentially improve neurological outcome from injury.

15. SUBJECT TERMS
AC-105, Magnesium, Mg, Spinal Cord Injury, SCI

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	11	**19b. TELEPHONE NUMBER** *(include area code)*

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1. INTRODUCTION:

Acorda therapeutics is developing AC105 for the treatment of acute spinal cord injury. This trial is partially supported by the funds from this Department of Defense Broad Agency Announcement for Extramural Medical Research grant. The primary hypothesis of this proposed study is that treatment of people with acute SCI with the polymer formulation of magnesium known as AC-105 will result in greater normalization of CNS Mg than treatment with MgCl2 or saline solutions and potentially improve neurological outcome from injury.

2. KEYWORDS:

KEYWORDS: Acorda, AC-105, spinal cord injury, acute, SCI, magnesium, clinical, Mg, neuroprotective, spinal, cord, injury

3. OVERALL PROJECT SUMMARY:

Injuries of the brain and spinal cord in both the military and civilian settings frequently leave patients with permanent and severe disability. Research has shown that tissue magnesium (Mg) is rapidly depleted in injured central nervous system (CNS), and this depletion correlates with the severity of injury in animal models (Heath and Vink, 1999). Exogenously delivered Mg reduces injury in animals (Kwon et al., 2009). Conventional systemic Mg therapy is limited by the inability to achieve sufficient CNS levels to be effectively neuroprotective. Medtronic, Inc. developed a Mg formulation that enhances Mg accumulation at the injury site while avoiding systemic toxicity. Acorda Therapeutics licensed this formulation, herein referred to as AC-105, which increases CNS Mg concentration and results in better outcomes in experimentally injured spinal cord (Kwon et al., 2009).

We have planned a Phase 2, double-blind, randomized, placebo-controlled study of AC-105, delivered by intravenous infusion, involving approximately 40 adults with acute SCI, where treatment can be initiated within 12 hours of injury. This study will be conducted at approximately 30 centers. We will assess feasibility of rapid enrollment and explore outcomes measures of neurological function which will be compared between patients treated with AC-105 and saline. Another goal of the study is to develop systems within each site to reduce the time to treatment to less than six hours. The actual therapeutic window is unknown as this is the first trial in human subjects with injury; however, non-clinical data confirms that earlier treatment results in better recovery.

The studies will determine if the novel Mg formulation of AC-105 is safe and well tolerated in people with acute SCI, can be delivered rapidly after injury and if there are trends towards improved outcomes. With success of these objectives and a positive signal on neurological recovery, Acorda intends to proceed to Phase 3 registration studies, following agreement with FDA on appropriate outcome measures. Should these studies be successful Acorda intends to explore the use of AC-105 in other forms of CNS trauma, including traumatic brain injury and stroke.

Project Phase 1 – Planning, site recruitment and initiation
Planning – A synopsis and protocol outline were prepared and reviewed with expert consultants. The full protocol was developed at Acorda and approved through the appropriate DoD mechanisms. The protocol was cleared through FDA. A meeting with FDA to discuss the protocol was denied.

Acorda formed a project team comprising all the required departments including R&D, Clinical Operations, Regulatory Affairs, Technical Operations (Manufacturing/CMC), Quality Assurance, Medical Affairs and Biostatistics. This team is organized by a dedicated project manager from our Project Management group. The execution of the clinical development plan is carried out by a dedicated clinical operations teams led by a clinical project manager. A clinical research organization (CRO) has been selected to perform site feasibility, selection, monitoring, project management and data management.

Drug supply: The active ingredient, magnesium chloride hexahydrate ($MgCl_26H_2O$) with a molecular weight of 203.3, is supplied by EMD Chemicals (subject to change) and complies with USP, FCC, EP and BP monographs. The excipient component, polyethylene glycol with a molecular weight of 3350 Daltons (PEG 3350), is manufactured by Dow Chemical Company and complies with NF, FCC and EurPh requirements.

Both the Magnesium and Excipient AC-105 components are provided in a sterile 0.45% Sodium chloride solution. The sodium chloride is sourced in USP, FCC, EP grade and granular form from Fisher Scientific (subject to change). Sterile water for injection is sourced in USP grade from Abbott (subject to change). The pH of the Magnesium and Excipient AC-105 solutions is adjusted to approximately 6.0 using either hydrochloric acid or sodium hydroxide. Both hydrochloric acid and sodium hydroxide are subjects of NF monographs.

The AC-105-Magnesium and AC-105-Excipient components are supplied by the sponsor to the investigational sites in separate glass vials. Additional data on product specifications, storage, stability and handling are provided within the IND and are part of the package insert.

Packaging Coordinators Inc. (formerly AndersonBrecon) and Citation Clinical Labeling Systems have been selected as the service provider for labeling, packaging and shipping investigational products (IP) to the sites, respectively. IP labels for vials for the Canadian sites were translated by Kern Corporation.

Project Phase 2 – Active phase of clinical study and 6 month follow-up.
Site recruitment: Acorda aims to initiate approximately 30 clinical sites in the United States and Canada. The first patient was enrolled in September 2013. See Key Research Accomplishments for details on site initiation and study progress.

In addition to completing and finalizing the protocol, the following study documents were developed:

- Pharmacy Manual

    - The Pharmacy Manual is used as a training tool and a reference for the sites for the dose preparation, administration and documentation; drug accountability and return.
- Site Instructions Manual
    - The Site Instructions Manual is a reference material for the sites which contains general information on randomization, unblinding procedures and safety reporting.
- Electronic Case Report Forms (eCRF)
    - The eCRF is a data collection tool used for data entry by the site staff.
- Monitoring Plan
- Project Plan
- Laboratory Manual
- Imaging Project Plan
- Investigator Site Operations Manual
- Medical Monitoring Plan
- Safety Management Plan
- Data Safety Monitoring Board (DSMB) Charter
- eCRF/Remote Data Capture Completion Guidelines
- Data Management Plan
- Edit Checks Specifications
- Data Quality Control Plan
- IXRS Quick Reference Guide

The following systems were developed place and went live:
- Interactive Randomization System
- Remote Date Capture (RDC)

Some changes to the protocol were made between the application and the final approval by DoD and FDA. The significant changes to the protocol are detailed below.

The *Objectives* of the trial in the draft protocol in the application were as follows:
Primary:
- To determine the feasibility of initiating AC-105 treatment in patients with acute spinal cord injury (SCI) within 6 hours of injury

Secondary:
- To evaluate the effects of AC-105, $MgCl_2$ and saline, on CSF and plasma levels of Mg^{2+}, PEG and biomarkers when administered within 6 hours after acute spinal cord injury (SCI) to patients with sensorimotor complete injury (ASIA Impairment Scale A).

- To assess the effects of AC-105 on recovery of sensorimotor function in patients with acute SCI.

The *Objectives* of the trial as per the final approved protocol are as follows:

- To determine safety and tolerability of AC105 following a regimen of 6 intravenous doses over 30 hours in patients with acute non-penetrating traumatic spinal cord injury (SCI)
- To obtain initial data on the effects of AC105 on the recovery of sensorimotor function in patients with acute traumatic SCI
- To measure a number of biomarkers of CNS injury in blood
- To evaluate the pharmacokinetics (PK) of AC105 in the patient population

Initially the plan was to enroll 60 patients total randomized equally to 20 patients in each of the following groups: AC-105, $MgCl_2$ and vehicle. The approved final protocol only includes 20 patients randomized to receive AC-105 or vehicle.

Other Changes in the protocol
Diagnosis and main criteria for inclusion:

- ASIA Impairment Scale A (neurologically complete injury) changed to include ASIA A, B and C

Data management and statistical analysis plans were established.

4. KEY RESEARCH ACCOMPLISHMENTS:

- Received comments from the FDA Oct 2012
- Investigators Meeting May 2013
- Received No Objection Letter (NOL) from Health Canada April 2013
- First site initiated Jun 2013
- First patient randomized Sep 2013
    - 13 Pre-screened
    - 1 Screen Failure
    - 1 Randomized
    - No SAEs
- Selected sites: 27

- **Sites initiated: 11**

  Stony Brook Medicine, New York Medical University of Wisconsin
  Queen Elizabeth II Health Services - Canada
  University of Kansas
  Regions Hospital, Minnesota
  Medical College of Wisconsin
  Carolinas Rehabilitation
  Vancouver General Hospital
  University of Pittsburgh
  University of Maryland
  Thomas Jefferson University Hospital

- **Pending DOD approval: 1**

  University of Nebraska Medical Center

- **Sites pending initiation: 13**

  1. Miller School of Medicine – Florida
  2. UMDNJ – New Jersey Medical College
  3. Denver Health Medical Center
  4. University of Nebraska Medical Center
  5. University of Southern California
  6. University of Texas – Houston
  7. Mt. Sinai Hospital
  8. St, Michael's Hospital, Ontario
  9. Toronto Western Hospital
  10. The Ottawa Hospital
  11. Baystate Medical Center, MA
  12. Indiana University Health Methodist Hospital
  13. Marshall Health, WV
  14. Parkview Regional Medical Center, IN
  15. Henry Ford Hospital Neuroscience Institute, MI

Protocol and Amendments

- Version 1.0 23Aug2012
- Version 2.0 14Dec2012
- Version 3.0 10Sep2013

The informed consent form template was amended to reflect protocol changes. New eCRF pages are being developed to capture data points from the protocol amendments.

Safety Refresher Training

- Safety refresher training is being conducted by Acorda Drug Safety and Risk Management with the sites.

- Held investigator meeting on May 9, 2013 in Chicago, IL.
    - Covered at the meeting: Introduction to Acorda, AC105 and Pre-clinical overview, Protocol Overview, Study Procedures and Timelines, SAE reporting, Medical Monitoring, GCP/ICH, Monitoring and Source Documentation, Unblinded Monitors, Blinded Assessors & Training, DSMB, Central Laboratory, MRI Central Reader, IXRS, Investigational product, Data Management

- Data Safety Monitoring Board (DSMB): An independent DSMB has been organized for this study and is comprised of five independent voting members and two nonvoting members from Acorda. A DSMB charter has been developed which outlines the roles and responsibilities of the DSMB members and the logistics of the safety data review meetings. The DSMB is managed by the CRO.

DSMB Charter and Amendments

- Version 1.0 06Feb2013
- Version 2.0 12Apr2013

DSMB Kick-off Meeting held on May 13, 2013 in Ardsley, NY. The DSMB charter was discussed at this meeting.

Study challenges:

To date there have been no significant challenges with execution of the study. The issues we have encountered involve finalization of contracts, IRB approval and site initiation. Acorda experienced a delay in shipment of the study drug due to availability of study drug containers (i.e. 500 ml bottles) and importation requirement for the Canadian site. Delays in initiating sites resulted from uncertainty from the sites about whether or not they each need to have a direct agreement or contract with DoD. Our contacts with DoD have been very helpful in explaining to sites that while DoD may be contacting them directly about the study, that all contracting will be done through Acorda. The second issue that has delayed initiation of the study at several sites is that the sites have asked us to increase the indirect funding rate from that which was initially negotiated with Acorda to reflect the indirect funding rate they receive from Federal grants. We are currently investigating how to manage this request as the DoD funds are only covering a

small percentage of the total costs, the indirect rate Acorda requests is lower and the indirect rates between Acorda and the sites were already negotiated.

Work to be performed during the next reporting period:

- Continue clinical trial agreement execution
- Continue collecting regulatory documents from sites
- Update the Pharmacy Manual to reflect changes in Protocol Amendment Version 3.0 and the new dose preparation procedures.
- Finalize new ECRF pages due to the Protocol Amendment Version 3.0
- Develop study awareness materials (e.g. study posters, magnets) for distribution to the sites.
- Select two sites (selected 28)
- Initiate remaining selected sites.
- Collect IRB/REB approvals for Protocol Amendment Versin 3.0 and submit to Department of Defense – Human Research Protection Office (HRPO)

5. CONCLUSION:

Acorda has initiated eleven sites and enrolled two patients. We experienced a delay in shipment of investigational product due to availability of investigational product containers; this issue has been resolved. Acorda continues to identify and initiate study site as well as eligible patients.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

N/A

7. INVENTIONS, PATENTS AND LICENSES

N/A

8. REPORTABLE OUTCOMES:

N/A

9. OTHER ACHIEVEMENTS:

N/A

10. REFERENCES:

Heath DL, Vink R. (1999) Concentration of brain free magnesium following severe brain injury correlates with neurologic motor outcome. J Clin Neurosci. 6(6):505-9.

Kwon BK, Roy J, Lee JH, Okon E, Zhang H, Marx JC, Kindy MS. (2009) Magnesium chloride in a polyethylene glycol formulation as a neuroprotective therapy for acute spinal cord injury: preclinical refinement and optimization. J Neurotrauma. 26(8):1379-93.

11. APPENDICES:

N/A

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