Principal Investigator

First Name: Anthony
Last Name: Daniels
Degree: BS
Primary Affiliation: UCB Biosciences
E-mail: datasharing.coordinator@ucb.com
Phone number: 919-767-6013
Address: 8010 Arco Corporate Drive

City: Raleigh
State or Province: NC
Zip or Postal Code: 27617
Country: USA

General Information

Key Personnel (in addition to PI):
First Name: Ting
Last name: Li
Degree: PhD Pharmaceutical Sciences
Primary Affiliation: UCB Biosciences
SCOPUS ID:

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Other

Conflict of Interest

http://yoda.yale.edu/system/files/coi-tony_daniels.pdf
http://yoda.yale.edu/system/files/yoda_coi_tli.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training
Associated Trial(s):

1. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children
2. NCT00113815 - A Randomized, Double-Blind, Placebo-Controlled, Fixed Dose-Ranging Study to Assess the Safety, Tolerability, and Efficacy of Topiramate Oral Liquid and Sprinkle Formulations as an Adjunct to Concurrent Anticonvulsant Therapy for Infants (1

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Development and validation of historical control using placebo data from pediatric epilepsy studies

Narrative Summary:

In the development of new drugs, pharmaceutical companies need to conduct clinical studies in the pediatric population for medications approved for the same indication in adults. To prove that the new treatment works in children, there needs to be a standard to which the new medication can be compared to show it performs better than no treatment. To limit the number of pediatric subjects exposed to placebo, it is proposed to perform a combined analysis of the placebo responses observed in completed studies in children with epilepsy to create a historical control for reference in future studies.

Scientific Abstract:

Background: Clinical studies in the pediatric population are often more difficult to enroll than those conducted in adults. Ethical questions arise about exposing children to placebo.
Objective: To create a historical control using the data from pediatric subjects for several anti-epileptic drugs (eg, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate) that could be used as a comparator to future drugs.
Study Design: A meta-analysis design is proposed to combine the results from multiple studies
Participants: Subjects from clinical studies that meet the following criteria:
• Randomized and placebo-controlled
• Has at least one of the main outcomes with aggregate statistics reported:
• Information is available on the number of treatment arms in the study and subjects randomized to each arm and corresponding dosages
• Subjects <18 years of age
• Specific indication (partial-onset seizures, generalized seizures)
• Type of therapy: adjunctive or monotherapy
Main Outcome: The main outcomes are the reduction in seizure frequency compared to baseline and percent reduction in seizure frequency from baseline (responder status)
Statistical Analysis Plan: A meta-analysis design is proposed to combine results from multiple studies. If participant-level data for applicable studies is available, modeling and simulation exercises may also be employed including evaluation of a Bayesian posterior distribution and validating previous results by substitution of historical placebo data.

Brief Project Background and Statement of Project Significance:

Clinical studies in the pediatric population are often more difficult to enroll than those conducted in adults; especially in the population of children younger than 4 years of age. To limit the number of pediatric subjects exposed to placebo in future studies, it is proposed to perform a meta- analysis of the placebo responses observed in completed studies in children with epilepsy (especially those with partial-onset seizures) to create a historical control (a group of patients who were observed at some time in the past or for whom data are available through records) for reference in future studies.

The significance of this analysis is that it could possibly reduce the number of pediatric subjects required to be randomized to the placebo arm of clinical studies, and would minimize the exposure of a larger number of pediatric subjects with potentially life-threatening seizures to placebo. In addition, leveraging historical control placebo response may shorten development timelines, allowing quicker access to additional treatment options for epilepsy in the pediatric population.

Specific Aims of the Project:

The goal of this proposal is to summarize the placebo response in pediatric patients randomized to placebo in, randomized, controlled studies of anti-epileptic drugs in children with epilepsy (particularly partial-onset seizures).

What is the purpose of the analysis being proposed? Please select all that apply.

Confirm or validate previously conducted research on treatment effectivenessParticipant-level data meta-analysisParticipant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Data will be obtained on subjects randomized to the placebo arm of randomized controlled studies. Specifically the analysis will focus on clinical studies that meet the following criteria:

• The study is randomized and placebo-controlled
• The study has at least one of the following efficacy endpoints as primary with aggregate statistics reported:
1. Reduction in seizure frequency compared to baseline
2. Percent reduction in seizure frequency from baseline (responder status)
• Information is available on the number of treatment arms in the study and subjects randomized to each arm and corresponding dosages
• Study includes subjects <18 years of age
• Specific indication (partial-onset seizures, generalized seizures)
• Type of therapy: adjunctive or monotherapy

Main Outcome Measure and how it will be categorized/defined for your study:

There are two primary endpoints of interest in this study.

1. The percent (%) reduction in seizure frequency from baseline (continuous variable)

2. Responder status (yes/no) where responder is defined as subjects with ?50% reduction in seizure frequency from baseline

The effect measure of interest is the placebo rate for the two efficacy endpoints.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The proposed analysis is to perform a meta-analysis of placebo response based on endpoints from completed clinical trial. The main predictor/independent variable is treatment (placebo).
Possible predictors of response and covariates that may be considered are : age, type of epilepsy, baseline seizure frequency, use of concomitant AEDs, number of concomitant AEDs, use of benzodiazepines, age of subject at time of epilepsy diagnosis, previous AED use, and country/region.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Other Variables of Interest may be defined once all available data is collected from YODA and data sources outside of YODA (eg, demographic information).

Statistical Analysis Plan:

Pediatric epilepsy study data will be included in this meta-analysis from various sources.

UCB will load data from the following studies into the SAS MSE via CSDR for analysis.
• N159
• N1009
• N1103

Additionally, data requests for the following companies and studies have been made and approved.

GSK (via CSDR, analyzed in SAS MSE):
• GSK-LAM100036
• GSK-LAM100034

• GSK-LAM40097
• GSK-LAM20006
• GSK-105-123
• GSK-105-040

Novartis (via CSDR, analyzed in SAS MSE):
• NOVARTIS-CTRI476E2339
• NOVARTIS-CTRI476E2340

Two studies are requested from YODA platform:
• Protocol YP
• NCT00113815

Aggregate data for efficacy endpoints from the requested studies will be used in a meta-analysis design is proposed to combine the results from multiple studies as a weighted average. Summary statistics for studies from the YODA system will be loaded into the SAS MSE for this analysis. The result of combing study results to form a new placebo historical control may increase the statistical power (over individual studies) and may, improve estimates of the size of the effect. An estimate of the combined placebo historical control for each endpoint will be evaluated using a fixed effect model. The inverse of the estimates' variance will be used as the study weight. Heterogeneity of studies will be investigated. Forest plots will be utilized to graphically depict the results.

If participant-level data for applicable studies is available, modeling and simulation exercises may also be employed. A Bayesian framework will be also be considered and evaluated. Estimated means and treatment differences along with 95% CIs will be used to develop a posterior distribution. The robustness of previous study results will be examined by substituting placebo arm data with the combined historical control participant level data down-weighted as appropriate.

Possible predictors of response and covariates that may be considered for subgroup analyses are : age, type of epilepsy, baseline seizure frequency, use of concomitant AEDs, number of concomitant AEDs, use of benzodiazepines, age of subject at time of epilepsy diagnosis, previous AED use, and country/region.

Project Timeline:

It is estimated that this project can be completed within a one year timeframe and will consist of the following timeframes: requesting and collection of data, completion of analysis, summarization of data, and submission of data to Regulatory Authorities.

Dissemination Plan:

After analysis is completed, the results would be submitted for publication to an epilepsy-related journal (eg, Epilepsia, Epilepsy Research, Journal of Pediatric Epilepsy) available to the public.

Bibliography:

Any references related to the included study data and statistical analyses (eg, statistical methodology, study publications for included studies) will be listed in the final publication.