MALLINCKRODT PHARMACEUTICALS, INC.INVESTIGATIONAL NEW DRUG PROTOCOL

Statistical Analysis Plan (SAP)

GABLOFEN® (baclofen injection) 3 MG/ML

Section 14 and 16

Templates for the Summary Tables, Figures, and Listings

Protocol: **CNS-GAB101US**

Version 1.3

STUDY TO ASSESS THE SAFETY OF 3 MG/ML GABLOFEN® (BACLOFEN INJECTION) DELIVERED BY INTRATHECAL ADMINISTRATION USING THE SYNCHROMED® II PROGRAMMABLE INFUSION SYSTEM

CONFIDENTIAL

Version 1.3

Date: 08 October 2015

Statistical Analysis Plan Approval

Title:	Study to Assess the Safety of 3 mg/mL Gablofen® (baclofen injection) Delivered by Intrathecal Administration Using the SynchroMed® II Programmable Infusion System
Protocol Number:	CNS-GAB101US
Owner:	Mallinckrodt Inc., Department of Biostatistics
Version Number	1.3
Version Date:	08 October 2015

The undersigned have reviewed this document and find that it meets the requirements with respect to the protocol.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CSF	Cerebral Spinal Fluid
CNS	Central nervous system
CO_2	Carbon dioxide
CRF	Case report form
CRU	Clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events (v. 4.03)
EC	Ethics Committee
ECG	Electrocardiogram
g	Gram
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice(s)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
Incidence	Number of subjects with one or more events
IRB	Institutional Review Board
IT	Intrathecal Injection
IP	Investigational Product
kg	Kilogram
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum Feasible Dose
mg	Milligram
mL	Milliliter

ABBREVIATION	DEFINITION
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NDA	New Drug Application
PI	Principal Investigator
Rate	Number of events adjusted for a unit of time
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
USP	United States Pharmacopeia
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) supports the evaluation of the protocol outcomes and planned assessments while 3 mg/mL concentration of Gablofen® (baclofen injection) is administered to subjects.

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses of the safety and frequency of inflammatory granuloma from a 3 mg/mL formulation of Gablofen® (baclofen injection). All analyses, quality control procedures, and data displays will follow the Global Statistical Group's standard operating procedure.

The content of this SAP is based on the revised protocol CNS-GAB101US version 2.0 (18 December 2014). Further information can be found in the study protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

The primary objective of this safety and post-approval surveillance study is to obtain data on the rate of inflammatory granulomas in patients given Gablofen® (baclofen injection) 3mg/mL by the intrathecal route of administration.

The secondary objective is to evaluate the overall safety data on 3 mg/mL Gablofen® (baclofen injection) given by the intrathecal route of administration.

2.1.1. Study Endpoints

2.1.1.1. Primary Endpoint

The primary endpoint is the rate of confirmed inflammatory granulomas after the first 12-months of therapy following the initiation of treatment with a 3 mg/mL formulation of Gablofen® (baclofen injection).

A confirmed inflammatory granuloma or mass is one where there are clinical signs and symptoms of an inflammatory granuloma, and an intradural extra-medullary mass is verified by an MRI with contrast enhancement. If only clinical signs and symptoms are identified, and no other assignable cause can be identified, the event will be recorded as a possible inflammatory mass.

All MRI-confirmed granulomas will be evaluated by a central independent radiologist as a routine trial procedure per the protocol.

Incidence is defined as the number of subjects with one or more events.

The rate of inflammatory granulomas will be evaluated based on 0 to 9 months, 0 to 12 months, and > 12 months of therapy.

For 0 to 9 months and 0 to 12 months of therapy, rate will be defined as:

$$\text{Rate} = I_T / (N_T + G_T)$$

Where:

I_T = Number of subjects with an inflammatory granuloma within the time interval
N_T = Number of subjects who reach the end of the time interval
G_T = Number of subjects with inflammatory granuloma who discontinue prior to reaching the end of the time interval

For > 12 months of therapy, rate will be defined as:

$$\text{Rate} = I_{>12} / N_{>12}$$

Where:

$I_{>12}$ = Number of subjects with an inflammatory granuloma after 12 months of therapy
$N_{>12}$ = Number of subjects who reach beyond 12 months of therapy

2.1.1.2. Secondary Endpoint

The secondary objective of this study is to evaluate the overall safety data on 3 mg/mL Gablofen® (baclofen injection) given by the intrathecal route of administration.

2.1.2. Safety and Tolerability Endpoints

Safety will be evaluated by the incidence of treatment emergent AEs and by changes in the physical examination findings and vital signs to the end of the treatment period. Adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA version 13.1). Also Medical History and Clinical evaluation for inflammatory mass formation will be included in the safety analysis.

The safety variables to be evaluated in this study are:

1. Adverse Event
2. Physical Exam
3. Vital Sign
4. Medical History
5. Clinical evaluation for inflammatory mass formation

These variables will be evaluated at the time points indicated in Schedule of Events in the protocol.

2.2. Statistical Hypotheses

No formal statistical hypotheses will be tested. Descriptive statistics will be used to assess safety and tolerability objectives.

3. STUDY DESIGN

This is a prospective twelve-month Phase IIIb clinical safety trial followed by 2-year, Phase IV study that will be conducted at 10 to 15 clinical trial sites that are experienced with the use of intrathecal baclofen. All subjects will be entered after signing an IRB approved informed consent. Subjects will be followed for the duration of their treatment with Gablofen® (baclofen injection) 3 mg/mL using the SynchroMed® II Programmable Pump or until the study is terminated. Subjects will be evaluated for clinical complications associated with the use of intrathecal baclofen that are considered signs and symptoms of an inflammatory granuloma, specifically new radicular pain at the level of the catheter tip, and/or spinal cord compression. Case report forms will be collected from the investigator at every clinical monitoring visit for the first 12 months for each subject enrolled and then every 6 months thereafter. If there are any signs or symptoms identified which may indicate an inflammatory granuloma formation, an MRI scan with and without infusion will be performed (with consent of the subject) to evaluate the potential presence of an inflammatory granuloma. Events that may be related to an inflammatory granuloma will be classified as definite granuloma, possible granuloma, or other catheter related problem (confirmed not caused by a granuloma) or other clinical sequelae caused by the underlying disease or infusion system related event. An interim analysis will be conducted when 100 subjects on the 3 mg/mL concentration of Gablofen® (baclofen injection) reach 9 months of treatment. Additionally, a second interim analysis will be completed after the first cohort of 100 subjects reach 12 months. Thereafter, annual safety reports will be generated as part of this 3 year program and a final study report completed when all subjects complete 36-months of treatment.

4. PLANNED ANALYSES

4.1. Interim Analysis

Two interim analyses will be conducted when 100 subjects reach nine (9) months of therapy and when 100 subjects reach twelve (12) months of therapy.

4.2. Final Analysis

The timing of the final analysis will be the end of the 36-month program. The final analysis will be completed following database freeze. Any changes from the planned analyses described in this section will be stated in the final study report.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Determination

Up to 150 subjects will be enrolled at up to fifteen investigative sites. The sample size for this study is not based on statistical considerations. The sample size was selected to ensure that 100 subjects will remain in the study for 12-months of evaluation.

5.2. Sample Size Re-estimation

A re-estimation of sample size will not be performed in this study.

6. ANALYSIS POPULATIONS

Safety Population

All subjects who were administered any amount of investigational product will be included in the analysis of safety.

Intent-to-treat (ITT) Population

The intent-to-treat (ITT) population will include subjects who were deemed eligible, have signed the informed-consent form (ICF) and treated with 3mg/ml baclofen.

Per-Protocol (PP) Population

The Per-Protocol population (PP) population will include subjects who were deemed eligible, signed the ICF, have been clinically evaluated for inflammatory granuloma formation through a physical examination evaluation of the investigator and receive therapy for at least 12 months and have no major protocol violations.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Data will be listed and summarized according to Social & Scientific Systems, Inc.'s reporting standards, where applicable.

Unless stated otherwise, descriptive summaries will include *N*, mean, standard deviation, median, minimum, and maximum for continuous variables and *N* and percent for categorical variables. For the change from baseline of continuous variables data, descriptive summaries will include *N*, mean, standard deviation, median, minimum, maximum, and *p*-value for the paired t-test or Wilcoxon signed-rank test (refer to section 10.8.1) between baseline and associated time point (p-values will be displayed only when

data is available for at least 10 subjects at that time point). Data will be summarized and reported. Version 9.1.3 or higher of the SAS™ system (SAS is a registered trademark of the SAS Institute, Inc., Cary, NC, USA) will be used to analyze the data as well as to generate tables, figures, and listings.

7.1. Multicenter Studies

Up to fifteen (15) investigative sites will participate in the study.

7.2. Other Strata and Covariates

There are no other strata and covariates.

7.3. Examination of Subgroups

A subgroup analysis will be performed for pediatric subjects and adult subjects. This will be done for the safety analyses of AEs, vitals, baseline physical examination, pump replacement, catheter replacement, and the incidence and rate of inflammatory granuloma.

8. DATA HANDLING CONVENTIONS

8.1. Premature Withdrawal and Missing Data

All subjects who withdraw from the study prematurely will be documented and the reason for their withdrawal will be reported in the final study report. Subjects who prematurely discontinue the study drug may be replaced. The study results up to the point of withdrawal for the withdrawn participant will be included in the data analysis. There is not any imputation method for missing data in this study.

8.2. Assessment Windows

Nominal times will be used for the descriptive summaries and plots of summary measures. Actual times will be used in the listings. Unscheduled screening and follow-up data will be excluded from statistical analyses. However, these data will be listed in the appropriate listings, summary tables, and summary plots.

8.3. Values of Clinical Concern

All changes in vital signs and abnormal values in physical examination and Clinical signs and symptoms that may indicate an inflammatory granuloma will be reviewed for clinical relevance by the Safety Review Team.

9. STUDY POPULATION

A Screening log of potential study candidates and an Enrollment log of subjects must be maintained at each study site. The general study population will consist of male and female subjects who are 4 years of age or older with severe spasticity and require intrathecal baclofen. Refer to the inclusion/exclusion criteria in the protocol for more detail.

9.1. Disposition of Subjects

Subjects will return to the clinic for safety evaluations and pump refills at least every 6 months or as dictated by their daily dose and need to refill the infusion pump. Subjects will also return at the nine (9) month time point for evaluations, even if the pump does not require refilling. Subjects who do not comply with the visit schedule will be discontinued from the study and pump refills continued with the approved concentrations of Gablofen® (baclofen injection). All data from enrolled subjects will be summarized to provide the number of subjects who complete the study treatment, and the number of subjects withdrawn, withdrawn due to AE, and withdrawn due to withdrawal of consent. Subject listing will be provided.

9.2. Protocol Deviations

Protocol deviations will be reported to Mallinckrodt Pharmaceuticals and will be documented in the clinical study report. Any changes from the analyses described within this statistical analysis plan will be stated in the final study report.

9.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics for the subject population will be listed and summarized by using the safety population, ITT and PP populations.

9.4. Treatment Compliance

Study medication will be administered under the supervision of the study personnel. Compliance will be recorded in the case report form (CRF) at each visit (date and time of administration of study medication). Treatment compliance will be summarized and listed.

10. SAFETY ANALYSES

No formal statistical analysis of the safety data will be conducted. Safety data will be descriptively summarized by treatment and presented in a tabular and/or graphical form.

10.1. Extent of Exposure

The exposure data will be a by-subject listing, including refilled volume with the dates and times. Summary of treatment for mean of original daily dose and changed dose will also be provided.

10.2. Adverse Events

All adverse events (AEs) will be coded and classified according to System Organ Class (SOC) Preferred Term and Reported Term, using MedDRA. All AEs (non-serious and serious) will be listed. A summary of the number and percent of subjects reporting each event at least once will be generated for all AEs and also for drug-related AEs. Adverse events by SOC and Preferred Term will be summarized by severity. A listing of the relationship of AE body systems, group terms and verbatim text will also be produced.

10.3. Clinical Evaluation for Inflammatory Mass

The incidence (number of subjects with one or more events), frequency and rate of inflammatory granulomas will be summarized for 0 to 9 months, 0 to 12 months, and > 12 months of therapy. All inflammatory granulomas data will be listed for each subject and data from any SAE reports relating to inflammatory granulomas will be summarized in full detail.

A summary of the incidence and frequency of inflammatory granulomas by classification (Confirmed and possible) will also be presented.

These analyses will be performed for both the ITT and PP populations. The ITT population will be the primary analysis population.

10.4. Deaths and Serious Adverse Events

Any deaths and other serious adverse events will be summarized and listed as appropriate to the data.

10.5. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

If any subject withdraws due to an AE, then a listing and a summary will be provided for these subject(s).

10.6. Pregnancies (as applicable)

Pregnancy test is not applicable for this study.

10.7. Other Safety Measures

10.7.1. Physical Examination

Baseline physical examination findings will be categorized by class variable (*i.e.*, normal or abnormal) and summarized by investigator determined body system. Clinically meaningful abnormalities found during physical examination (that were not present or have worsened since baseline) will be reported and analyzed as AEs.

10.7.2. Medical History

All medical history data will be listed for each subject.

10.7.3. Vital Signs

All vital sign data will be listed for each subject. A descriptive summary including change from baseline will be presented at the 6-month, 9-month, 12-month, and 36-month visits for the vital signs.

10.8. Statistical Method for Analysis of Safety and Demographic data

10.8.1. Wilcoxon Signed-rank Test

The Wilcoxon signed-rank test is a non-parametric statistical hypothesis test for the case of two related samples or repeated measurements on a single sample. It can be used as an alternative to the paired Student's *t*-test when the population cannot be assumed to be normally distributed. Like the paired or related sample *t*-test, the Wilcoxon test involves comparisons of differences between measurements, so it requires that the data are measured at an interval level of measurement. However, it does not require assumptions about the form of the distribution of the measurements. It should therefore be used whenever the distributional assumptions that underlie the *t*-test cannot be satisfied. This test will be used to test the difference between baseline and visit in case the variables are continuous. SAS code such as that below will be used to fit the method described above:

```
PROC UNIVARIATE;
  VAR chage;
 RUN;
```

10.8.2. 95% Confidence Interval

The incidence (number of subjects with one or more events) of inflammatory granulomas, suspected granulomas, and other catheter related events will be summarized and a 95% CI of the percent of subjects with one or more events will be presented. The rate of subjects with inflammatory granulomas for 0 to 9 months, 0 to 12 months and > 12 months therapy period will be summarized including a 95% CI of the mean rates. Results will be summarized in the three planned interim reports and included in the overall study final report at the end of 3 years.

11. REFERENCES

1. ICH E6 Good Clinical Practice: Consolidated Guidance. ICH, 1996.