INVESTIGATIONAL NEW DRUG PROTOCOL

GABLOFEN® (baclofen injection) 3 MG/ML

PROTOCOL NUMBER CNS-GAB101US

VERSION 1.1 DATED 13 MAY 2013

VERSION 2.0 DATED 18 DECEMBER 2014

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

SPONSOR:

MALLINCKRODT PHARMACEUTICALS INC.

675 MCDONNELL BLVD

HAZELWOOD, MO 63042

USA

CONFIDENTIAL

SUMMARY OF CHANGES FROM VERSION 2.3 TO VERSION 3.0

DATED 18 DECEMBER 2014

This protocol amendment was required to change the sponsor from CNS Therapeutics, Inc. to Mallinckrodt Pharmaceuticals, Inc., the SAE reporting information and contact personnel from Pacific Link Consulting to Mallinckrodt, and to assign a new medical monitor. These and other changes are listed below:

1. Version is changed from v1.1 to v2.0 and protocol re-dated as appropriate. Title page, headers and footers, and protocol text are revised as appropriate to reflect the new sponsor.

2. Section 13.1 was changed to provide a new medical monitor and medical monitor contact information.

3. Section 13.2.1 and Table 13-3 were changed to provide current Mallinckrodt procedures for handling serious adverse events and Mallinckrodt contact information.

4. Section 14.4 (Safety) was changed for coding of AEs to include presentation by body system and preferred term, rather than just body system. A sentence indicating summarization of lab abnormalities at each time point for each cohort was deleted, since labs are not collected in this study beyond baseline. Summarization of prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class but not by dose cohort. A sentence was added to indicate that safety analyses will be presented by age group (pediatric and adult) and for all subjects. Section 14.4 updates were made in order to be consistent with the approved statistical analysis plan.

5. Minor edits were made to correct grammar and spelling errors.

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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
CRF	Case report form
CRU	Clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events (v. 4.03)
EC	Ethics Committee
FDA	Food and Drug Administration
g	Gram
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice(s)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IT	Intrathecal Injection
ITT	Intent-To-Treat
IP	Investigational Product
kg	Kilogram
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Microgram
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
SAE	Serious Adverse Event
U.S.	United States (of America)
USP	United States Pharmacopeia
WHODD	World Health Organization Drug Dictionary

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INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonization Good Clinical Practice Guidelines E6 (ICH-GCP, 1996).

I will maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 13.2 of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the medical monitor for approval prior to enrollment of the subject in the study.

I will allow the Sponsor, Mallinckrodt Pharmaceuticals, Inc. and its agents, as well as the United States (U.S.) Food and Drug Administration (FDA) and other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than 1 week).

The contents of this protocol may be disclosed to study personnel under your supervision and to your IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Mallinckrodt Pharmaceuticals, Inc.

_____ _____

Investigator's Signature Date

PROTOCOL SYNOPSIS (PAGE 1 OF 3)	
Study Title	Study to Assess the Safety of 3 mg/mL Gablofen® (baclofen injection) Delivered by Intrathecal Administration Using the SynchroMed® II Programmable Infusion System (CNS-GAB101US)
Phase	IIIb (Open-label Safety)
Study Drug	Gablofen® (baclofen injection)
Objectives	Primary objective: • 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. Secondary objectives: • To evaluate the overall safety data on 3 mg/mL Gablofen® (baclofen injection) given by the intrathecal route of administration.
Study Design	This is a prospective twelve-month Phase IIIb clinical safety trial followed by a 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 patients will be entered after signing an IRB approved informed consent. Patients 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. Patients 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. Reports will be requested from the investigator at every clinical visit for the first 12 months for each patient 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 patient) to evaluate the potential presence of an inflammatory granuloma. Events that may be related to an inflammatory granuloma will be classified as a definite granuloma, possible granuloma, other catheter related problem (confirmed not caused by a granuloma), or other clinical sequelae caused by the underlying disease or other 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 safety update will be provided to the FDA after the first cohort of 100 patients reach 12 months. Thereafter, annual reports to the NDA will be generated and provided to the FDA as part of this 3-year program.
Sample Size	Up to 150 subjects enrolled (100 completers at 12-months)
Study Population	Male or female subjects 4 years of age or older with severe spasticity and who are being treated with intrathecal baclofen.

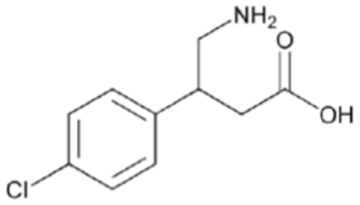
PROTOCOL SYNOPSIS (PAGE 2 OF 3)	
Main Inclusion Criteria	1. 4 years of age or older 2. Subjects must be clinically diagnosed with severe spasticity and be receiving intrathecal baclofen 3. Subjects must have a SynchroMed® II Pump already implanted 4. Current treatment with intrathecal baclofen should be at the 2 mg/mL concentration 5. Life expectancy ≥ 12 months 6. Signed written informed consent 7. Ability and willingness to comply with the study protocol for the duration of the study and with follow-up procedures
Main Exclusion Criteria	1. History or presence of malignancy, with the exception of adequately treated localized skin cancer (basal cell or squamous cell carcinoma) or carcinoma in-situ of the cervix, which is allowed 2. History of any allergic reaction to baclofen 3. History of inflammatory granulomas with an intrathecal infusion pump 4. Any previous history of neuroleptic malignant syndrome or malignant hyperthermia 5. As a result of medical review and physical examination, the Investigator considers the subject unfit for the study
Dosage and Administration of Study Drug	Subjects will be on a stable regimen of intrathecal baclofen at a concentration of 2 mg/mL. After qualification, the remaining baclofen in the SynchroMed® II Pump will be removed and the pump will be loaded with 3 mg/mL Gablofen® as per normal filling requirements for a SynchroMed® II Pump. Patients will be monitored by the physician and examined at least every 6 months for the 3-year duration of the study for any indications of complications with the device or clinical signs and symptoms of concern. More frequent visits to the investigating physician may be necessary for pump refills depending on the daily dose of baclofen. The total daily dose in this trial will not exceed 2000 mcg/day. A safety evaluation and adverse event reports will be requested from the investigator at every clinical visit for the first 12 months for each patient enrolled and then every 6 months thereafter based upon a pre-defined schedule of events.
Safety Analysis	Subjects will be assessed throughout the study for adverse events and potential clinical signs and symptoms of an inflammatory granuloma. Safety will be assessed through collection of AEs and SAEs during the conduct of the trial. At each visit, the subject will be queried for any AEs that differ from their baseline condition at the time of enrollment into the trial. The use of intrathecal opioids has been associated in rare cases with an inflammatory granuloma at the catheter tip that can result in serious neurological impairment, including paralysis. While these events have not been reported with commercial baclofen that has been unaltered by pharmacy compounding, the potential for an inflammatory granuloma with higher concentrations of baclofen has not been assessed. In this study, the potential for an inflammatory granuloma will be assessed at each visit to the investigator.

PROTOCOL SYNOPSIS (PAGE 3 OF 3)	
Safety Analysis (Cont.)	Clinical signs and symptoms that may indicate an inflammatory granuloma include: o a sudden decrease in therapeutic response requiring increased daily doses that is not attributed to other assignable causes (e.g. mechanical failures, catheter movement or catheter blockages) o unexplained pain at the dermatomal level of the catheter tip o unexplained neurological deficit or dysfunction that could be due to compression of the spinal cord at the level of a catheter tip For the purpose of this study, definite inflammatory granuloma is an intramural extra-medullary mass at the catheter tip that is confirmed by an infusion MRI. If only clinical signs are detected, but the inflammatory granuloma or mass cannot be verified by MRI, and no other cause can be determined, the event will be classified as a possible inflammatory granuloma. If in the opinion of the investigator there is a reasonable probability that the subject may be experiencing an inflammatory granuloma, an MRI without and with infusion of a contrast agent will be requested. All MRIs will be assessed by a single central independent radiologist who will be blinded to the patient's history. During the trial, all SAEs reported to the investigator shall be reported to the Mallinckrodt Pharmacovigilance department within 24 hours of the event being reported to the investigator. The investigator will be asked to provide details of the SAE, an assessment of severity of the event and an opinion as to relatedness to study medication or to other causes. Safety data from the study will be analyzed by the nature, frequency, and severity of drug related serious adverse events for all subjects including at baseline, within study, and the end of study. Demographic information will be presented for each subject and summarized. Treatment-emergent adverse events and relevant laboratory results will be summarized. Events of inflammatory granuloma's will be described both as part of the descriptive statistics, and each event will include a full narrative assessment including MRI reports, clinical interventions and outcome. Data will be presented as summary statistics. The intent-to-treat (ITT) population includes all patients who were deemed eligible, have signed the informed-consent form (ICF) and treated with 3 mg/mL baclofen. The evaluable (or "per protocol") population is the subset of ITT patients who were deemed eligible, signed the ICF, have been clinically evaluated for inflammatory granuloma formation through a physical examination and evaluation of the investigator. The incidence of definite inflammatory granulomas, possible granulomas, and other catheter related events will be summarized in annual reports for 3 years.
Efficacy Analysis	There is no efficacy measure in this open-label clinical trial. However, the dose of baclofen intrathecal will be monitored during the trial.
Study Duration	It is planned that each subject will participate in the study for a minimum of 12 months with an extension for up to 24 additional months permitted at the discretion of the patient and attending physician. Overall duration of the study will be approximately 48 months, depending on the rate of enrollment and number of subjects enrolled.
Study Centers	Up to fifteen (15) investigative sites will participate in the study.

1.0 INTRODUCTION

1.1 Background

Baclofen (Gablofen®) is a derivative of gamma-aminobutyric acid (GABA) and is an agonist for the $GABA_B$ receptors (Mezler et al., 2001; Dzitoyeva et al., 2003). It is primarily used to treat spasticity and has been a primary treatment for this indication by both oral and intrathecal routes of administration. Baclofen's beneficial effects in spasticity result from actions at the spinal level. Baclofen does not seem to significantly induce tolerance and maintains its anti-spasmodic effect over many years. However, if the underlying disease that is the source of the spasticity continues to progress, the dose of baclofen needed to manage the spastic symptoms may increase over time.



Baclofen USP

Gablofen® (baclofen injection) is indicated for use in the management of severe spasticity in adult and pediatric patients age 4 years and above. Gablofen® (baclofen injection) is currently approved only for use in the Medtronic SynchroMed® II Programmable Pump or other pumps labeled for intrathecal administration of Gablofen® (baclofen injection). The pump is refilled with Gablofen® (baclofen injection) using an appropriate refill kit and according to the pump manufacturer's instructions. Gablofen® (baclofen injection) or other baclofen products are not permitted by labeling to be compounded with other medications for the purpose of intrathecal administration.

After confirmation of the efficacy of Gablofen® (baclofen injection) by intrathecal injection, an infusion pump may be implanted. The dose may be adjusted by intrathecal injection until the desired clinical effect is obtained. After implantation of a SynchroMed® II pump, the dose titration of Gablofen® (baclofen injection) may be adjusted to obtain the optimal clinical effect.

Over time, the dose of Gablofen® (baclofen injection) may be increased by up to 20% each time the pump is refilled. Sudden changes in dose may indicate a catheter complication and should be carefully evaluated and corrective actions taken as appropriate. At the higher doses, the frequency of pump refills can become a burden on the patient and medical system. Thus, a higher concentration formulation of Gablofen® (baclofen injection) is needed to help reduce the number of pump refills and improve patient quality of life.

The purpose of this study is to evaluate the safety of a higher concentration, 3 mg/mL of Gablofen® (baclofen injection).

The benefit and risks of intrathecal (IT) baclofen are well understood from many years of clinical experience and peer-reviewed publications. Medtronic has conducted a large publicly available post-approval surveillance study for the SynchroMed® II Programmable Pump that also includes surveillance of various drug products delivered by IT administration. This study followed 4,384 patients with implanted SynchroMed® II Programmable Pump drug delivery systems at fifty (50) centers, with 3,101 patients receiving various other IT medications for pain and 1,283 patients receiving baclofen for spasticity. Included in Medtronic's study was a careful examination of inflammatory granuloma formation in patients. An inflammatory granuloma in the Medtronic surveillance study was defined as "an intradural extra-medullary mass at the catheter tip that could be visualized by enhanced MRI imaging." The criteria for diagnosing such a granulomatous mass is based on several clinical signs and symptoms: a decrease of drug effect and new radicular pain and/or cord compression, MRI findings of an enhancing mass at the catheter tip on the T-1 infusion and surgical or histological confirmation.

From 2003 to 2010 six (6) cases of confirmed or probable inflammatory granuloma were noted as well as six (6) cases of possible granuloma out of the 4,384 patients evaluated (12/4384, 0.27%). All of these patients were being treated with intrathecal morphine for severe, intractable pain. Of particular note is that no cases of a granuloma (possible, probable or confirmed) were documented in the 1,283 patients who were receiving baclofen (0.0%). While it is well known that a significant amount of pharmacy compounding occurs to provide concentrations of baclofen up to 4 mg/mL in routine use, the number of patients receiving doses of baclofen above 2 mg/mL or multiple medications is not provided in the report. Thus, while the study clearly demonstrated that IT baclofen is not associated with inflammatory granuloma formation, and that the risk is far less than with IT morphine or morphine related drugs used in the SynchroMed® II Programmable Pump, no definite conclusions can be reached about the risk of the concentrations above 2 mg/mL from this study.

These data are further supported by published literature studies in peer reviewed journals that suggest inflammatory granuloma formation is not a significant risk with baclofen even at concentrations above 2 mg/mL (see the FDA Summary Basis of Approval for Gablofen® (baclofen injection) review pages 41-49 and (Deer et al., 2008)). The use of pharmacy compounded concentrations of baclofen above 2 mg/mL is common, but not well documented. The dangers of compounding of baclofen have been well illustrated (Moberg-Wolff, 2009) but inflammatory granulomas seem to occur only when opiates are co-infused with baclofen (Deer et al., 2008).

Medtronic has correctly warned physicians using IT baclofen therapy to avoid higher concentrations above 2 mg/mL given the implications of off label use, despite having no well documented cases of inflammatory granuloma formation in the FDA AERS database or published in the literature (PubMed search 8-2011). While no well-documented cases have been

reported, in a published review article by Deer et al., three (3) cases of possible inflammatory granuloma formation are reported based on reduced flow of solution through the catheter (Deer et al., 2008). However, he concludes that these cases cannot be confirmed as the reports did not included any confirming pathology, no T-1 enhancing mass at the catheter tip and no neurological signs of cord compression. The Deer et al. review article also noted that the only clinical complication was a gradual decrease in efficacy in the three (3) cases which was resolved by moving or changing the catheter to re-establish drug delivery. Thus, Deer and co-authors conclude that these cases were more likely due to "poor distribution of baclofen in the IT space where arachnid loculations, adhesions or encasement of the catheter tip are assumed to be the problem". It is important to note in evaluating clinical risk in these three (3) cases that even with reduce catheter flow, there were no symptoms of sudden withdrawal from baclofen and the patients were adequately treated without any long term negative clinical effects.

Thus, there is no clear signal in clinical trials, published literature, or 19 years of commercial use of IT baclofen that inflammatory granuloma formation is a meaningful clinical risk. It is also well known that physicians and pharmacists routinely provide higher concentrations of compounded baclofen for use in the SynchroMed® II Programmable Pump and other IT pumps. The risk of these compounded formulations that are not manufactured under GMP conditions and controlled for sterility would seem to present a more significant risk to patients than the undetectable risk of inflammatory granuloma formulation in this population (Moberg-Wolff, 2009). Given the effectiveness of baclofen in the management of severe spasticity of cerebral and spinal origin in adult and pediatric patients, the risk benefit profile for the use of this product provides the importance of replacing compounded higher strength formulations with a well-controlled commercial product would seem positive.

Mallinckrodt has developed a 3 mg/mL concentration of Gablofen® (baclofen injection) to meet the needs of patients on high daily doses and proposes this open label safety surveillance study to assess the potential for complications related to this higher concentration formulation.

1.2 Nonclinical Assessments

1.2.1 Pharmacology

The precise mechanism of action of baclofen as a muscle relaxant and anti-spasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and may exert its effects by stimulation of the $GABA_B$ receptor subtype. Baclofen when introduced directly into the intrathecal space permits effective CSF concentrations to be achieved with resultant plasma concentrations 100 times less than those occurring with oral administration. In people, as well as in animals, baclofen has been shown to have general CNS depressant

properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

1.2.2 Toxicology

1.2.2.1 Mutagenic and Carcinogenic Toxicity

No increase in tumors was seen in rats receiving baclofen orally for two (2) years at approximately 30 - 60 times on a mg/kg basis, or 10 - 20 times on a mg/m^2 basis, the maximum oral dose recommended for human use. Mutagenicity assays with baclofen have not been performed.

1.2.2.2 Genetic and Teratogenicity Studies

Specific genetic, fetal and post-natal toxicity studies have not been performed with baclofen. While the intrathecal route of administration gives low systemic exposure relative to oral baclofen, the potential for genetic or teratogenic effects cannot be ruled out.

1.3 Clinical Experience

Evidence supporting the efficacy of intrathecal baclofen was obtained in randomized, controlled investigations that compared the effects of either a single intrathecal dose or a three (3) day intrathecal infusion of intrathecal baclofen to placebo in patients with severe spasticity and spasms due to either spinal cord trauma or multiple sclerosis. Intrathecal baclofen was superior to placebo on both principal outcome measures employed: change from baseline in the Ashworth rating of spasticity and the frequency of spasms.

The efficacy of intrathecal baclofen was investigated in three (3) controlled clinical trials; two (2) enrolled patients with cerebral palsy and one enrolled patient with spasticity due to previous brain injury. The first study, a randomized controlled cross-over trial of 51 patients with cerebral palsy, provided strong, statistically significant results; intrathecal baclofen was superior to placebo in reducing spasticity as measured by the Ashworth Scale. A second cross-over study was conducted in 11 patients with spasticity arising from brain injury. Despite the small sample size, the study yielded a nearly significant test statistic ($p= 0.066$) and provided directionally favorable results. The last study, however, did not provide data that could be reliably analyzed.

1.4 Study Rationale

The rationale for the proposed open-label clinical safety surveillance study is to obtain safety data on a new higher concentration (3 mg/mL) of Gablofen® (baclofen injection). The study will provide safety data on at least 100 patients receiving the high concentration formulation for at least 12 months in support of a marketing authorization application to the US Food and Drug Administration.

The study design allows participants to utilize a higher strength concentration of Gablofen® (baclofen injection), which will allow less frequent pump refills. The study is open-label and as such all subjects will benefit from the higher strength formulation. Subjects will be monitored for safety at least every 6-months. While there is no expectation that complications will occur, if there are clinical signs of an inflammatory granuloma the subject will be asked to have an MRI to confirm the presence of a granuloma or to identify the cause of the symptoms which may be related to a blocked catheter or other pump related complication.

Thus, the study will provide adequate clinical safety data to allow for approval of this higher concentration formulation of Gablofen® (baclofen injection) that is manufactured under GMP controls and is a safer alternative to current pharmacy compounded products.

2.0 PURPOSE AND STUDY OBJECTIVES

2.1 Purpose

The purpose of this study is to confirm the safety and frequency of inflammatory granuloma from a 3 mg/mL formulation of Gablofen® (baclofen injection).

2.2 Study Objectives

2.2.1 Primary Objective

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.

2.2.2 Secondary Objectives

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.

3.0 STUDY DESIGN

3.1 Description of Trial Design

This is a prospective twelve-month Phase IIIb clinical safety trial followed by a 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 patients will be entered after signing an IRB approved informed consent. Patients will be followed for the duration of their treatment with Gablofen® (baclofen injection) 3mg/mL using the SynchroMed® II Programmable Pump or until the study is terminated. Patients 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.

Reports will be requested from the investigator at every clinical visit for the first 12 months for each patient 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 patient) 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 safety update will be provided to the FDA after the first cohort of 100 patients reach 12 months. Thereafter, annual reports to the NDA will be generated and provided to the FDA as part of this 3 year program.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is rate of definite inflammatory granulomas during 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 enhancement on an infusion MRI. 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.

3.2.2 Secondary Endpoints

The secondary endpoint of this study is to assess the overall safety during the first 12-months of therapy following the initiation of treatment with a 3 mg/mL formulation of Gablofen® (baclofen injection).

3.3 Diagnosis of an Inflammatory Granuloma

The use of intrathecal opioids has been associated in rare cases with an inflammatory granuloma at the catheter tip that can result in serious neurological impairment, including paralysis. While these events have not been reported with commercial baclofen that has been unaltered by pharmacy compounding, the potential for an inflammatory granuloma with higher concentrations of baclofen has not been assessed. In this study, the potential for an inflammatory granuloma or mass will be assessed at each visit to the investigator.

Clinical signs and symptoms that may indicate an inflammatory granuloma include:

- a sudden decrease in therapeutic response requiring increased daily doses that is not attributed to other assignable causes (e.g. mechanical failures, catheter movement or catheter blockages)
- change in the character, quality, or intensity of spasticity
- unexplained pain at the dermatomal level of the catheter tip
- unexplained neurological deficit or dysfunction that could be caused by mass effect at the spinal level of the catheter tip

For the purpose of this study, to establish that there is a definite inflammatory granuloma, an infusion MRI must demonstrate an intradural extra-medullary mass near the catheter tip. If only clinical signs are detected, but the inflammatory granuloma or mass cannot be verified by MRI, and no other cause can be determined, the event will be classified as a possible inflammatory granuloma.

If in the opinion of the investigator there is a reasonable probability that the subject may be experiencing an inflammatory granuloma, an MRI without and with infusion of a contrast agent will be requested. All MRIs will be assessed by a single central independent radiologist who will be blinded to the patient's history.

3.3.1 Treatment of an Inflammatory Granuloma

If an inflammatory granuloma is detected early in its clinical course, depending upon an individual patient's clinical condition, intraspinal therapy may be continued after one of the following interventions:

- Withdraw the catheter to a level below the inflammatory granuloma.
- Remove the involved catheter and replace it with a new catheter positioned below the inflammatory granuloma.
- Disconnect the involved catheter from the connector (two-piece catheter), or transect the involved catheter above the level of the lumbo-dorsal fascia (one-piece catheter) leaving the intraspinal catheter segment undisturbed. Ligate the exposed end of involved catheter to prevent CSF loss. Implant a new catheter with its tip below the inflammatory granuloma, and connect the new catheter to the proximal (pump) catheter segment.

Prompt open surgical removal of the granuloma or decompression of the spinal cord should be considered in patients who have a significant or progressive neurological deficit.

Regardless of interventions, if a granuloma is detected, the subject should be discontinued from this investigational trial and treated with conventional baclofen therapy.

3.4 Measures to Minimize Bias

3.4.1 Blinding

This study is not randomized and has no concurrent controls. Study drug will be administered in an open-label fashion.

3.4.2 Assignment to Study Drug

Each subject who is determined to be eligible for the study will be assigned a unique treatment number consisting of S for the site number and a three-digit subject number (SXX-XXX) by the by the study coordinator or designee. The subject number will be sequential at each clinical site

3.5 Study Drugs

3.5.1 Rationale for Doses and Dosing Regimen

All subjects enrolled in this trial will be on a stable current dose of intrathecal baclofen 2 mg/mL. A stable dose of baclofen for the purpose of this trial will be defined as adequate symptom control with no more than a 20% change in daily dose over a 30 day period. Study participants will be switched to the 3 mg/mL formulation of Gablofen® (baclofen injection) at their current daily dose of baclofen. Dose adjustments may be permitted ten (10) days after the switch to 3 mg/mL Gablofen® (baclofen injection) as needed according to standard of care, however, the daily dose will not exceed 2000 mcg.

3.5.2 Dosages and Dosing Regimen

3.5.2.1 12-Month Course of Treatment

Subjects in this trial will be enrolled at their current stable dose of baclofen. Dose adjustments will be permitted after ten (10) days on the 3 mg/mL Gablofen® (baclofen injection) formulation. The subject shall return to the investigational site for evaluation at least at 6, 9, and 12 months (± 7days). More frequent visits may be necessary for pump refills depending on the dose of baclofen administered daily.

3.5.2.2 Continuation of Therapy

In the absence of any significant side effects or other complications, treatment with Gablofen® (baclofen injection) 3 mg/mL may continue after the initial 12-month period for up to a total of 36 months. During the 24-month extension of therapy, subjects must return to the clinical site at least every 6 months for evaluation and pump refills. More frequent visits may be required for very high daily dose treatments where the pump will have to be refilled more than every 6 months.

3.5.3 Dose Modifications

Dose modifications are permitted after 10 days on the 3 mg/mL Gablofen (baclofen injection) formulation. Dose modifications will be done according to standard of care for patients on intrathecal baclofen. Given that the daily dose is not impacted by use of the higher concentration of Gablofen® (baclofen injection), no special dosing instructions are provided. Please see the current approved Gablofen® (baclofen injection) product labeling for dose modification instructions.

3.5.4 Dose Interruption

Dose interruptions are permitted for up to 10 continuous days for subjects on this clinical trial. This dose interruption may be necessary to correct catheter failures, replace pumps, to allow for a drug holiday or other medically documented reasons. Any dose interruption that exceeds 10 consecutive days will result in the subject being discontinued from the study, unless approved in advance by the Medical Monitor. Oral baclofen therapy may be prescribed at any time during an intrathecal medication dose interruption, surgical procedure or post-surgery period until the subject is stabilized on intrathecal baclofen therapy.

3.5.5 Pump or Catheter Replacements

Pump or catheter replacements are permitted in this trial due to mechanical malfunctions, battery failures or other related mechanical reasons. The Medical Monitor should be notified if any subject requires a surgical procedure to correct a catheter failure or requires a pump replacement.

If a subject requires a pump replacement or catheter replacement, dose interruptions for up to 10 days are permitted while the procedure is conducted and until study drug can be replaced into the new pump. If the pump is removed, study drug within the pump should be removed and the volume removed entered on the drug accountability log. When the pump is replaced, refill with investigational product from a new syringe of 3 mg/mL baclofen. After the pump or catheter replacement, at the discretion of the investigator, subjects may be restarted at their previous dose of baclofen or a reduced dose and titrated back to an optimal dose as part of normal standard of care for that subject. Oral baclofen therapy may be prescribed at any time during an intrathecal medication dose interruption, surgical procedure or post-surgery period until the subject is stabilized on intrathecal baclofen therapy.

For pump replacements that are performed at a medical institution that is unaffiliated with the study investigator's site, the investigator is responsible ensuring that study drug is removed from the pump and the waste is accounted for on the drug accountability log. The Investigator is responsible for contacting the responsible clinician performing the pump replacement to ensure they are aware the subject is involved in a clinical trial. After the surgery, the pump should be filled with either 2 mg/mL commercial (i.e. FDA approved) baclofen or saline until the subject can return to the investigators site to have the baclofen replaced with 3 mg/mL investigational product. If the subject cannot return to the investigators site within 10 days of a dose

interruption they will be discontinued from the study unless a longer dose interruption period is approved by the Medical Monitor in advance.

3.6 Concomitant Medications

3.6.1 Prior and Concomitant Medications

Prior medications are defined as medications that were taken within 30 days of the initial dosing with study drug.

Concomitant medications are defined as medications taken any time after the start of dosing through the 12 month visit. Concomitant medications are not collected after 12 months as part of this protocol.

There is inadequate experience with the use of intrathecal baclofen in combination with other medications to predict specific drug-drug interactions. Interactions attributed to the combined use of intrathecal baclofen and epidural morphine include hypotension and respiratory depression.

3.6.2 Prohibited Concomitant Medications

It is prohibited to combine as one solution for intrathecal administration, Gablofen® (baclofen injection) with other drugs. There are no other prohibited medications given by routes of administration other than intrathecal infusion.

3.7 Duration of Therapy

In the absence of an inflammatory granuloma or drug related SAE (serious adverse drug reaction) subjects in this trial may continue on treatment with 3 mg/mL Gablofen® (baclofen injection) for up to 36 months. An interim analysis will be conducted after 9 and 12 months of therapy.

3.8 Procedures for Monitoring Subject Compliance

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 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).

4.0 STUDY POPULATION

Male or female subjects 4 years of age or older with severe spasticity and requiring intrathecal baclofen.

4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for this study:

1. 4 years of age or older.
2. Must be clinically diagnosed with severe spasticity and are receiving intrathecal baclofen.
3. Must have a SynchroMed® II Pump already implanted.
4. Current treatment with intrathecal baclofen should be at the 2 mg/mL concentration.
5. Life expectancy ≥ 12 months.
6. Signed written informed consent.
7. Ability and willingness to comply with the study protocol for the duration of the study and with follow-up procedures

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. History or presence of malignancy, with the exception of adequately treated localized skin cancer (basal cell or squamous cell carcinoma) or carcinoma in-situ of the cervix, which is allowed
2. History of any allergic reaction to baclofen
3. History of inflammatory granulomas with an intrathecal infusion pump
4. Any previous history of neuroleptic malignant syndrome or malignant hyperthermia
5. As a result of medical review and physical examination, the Investigator considers the subject unfit for the study

5.0 SAFETY ASSESSMENTS

5.1 Collection of Adverse Events Data

Data regarding treatment-emergent AEs will be collected in this study. Treatment-emergent AEs are events that are not present at baseline, or if present at baseline, have worsened in severity. AEs will be assessed at each study visit from the time of study drug administration on Study Day 1 through the final visit. AEs assessed by the Investigator as related to study drug and "ongoing" at the final scheduled study visit will be monitored by the Investigator until resolved or stabilized.

Each subject will be observed and queried by the Investigator or his/her designee at each study visit for any continuing AEs or new AEs since the previous visit. If an AE occurs between study visits, regardless of causal relationship to study drug and in the opinion of the Investigator,

requires a study visit for full evaluation, the subject will be asked to return to the site for an unscheduled visit.

Any AE reported by the subject or noted by the Investigator or his/her designee will be recorded on the CRF. The following information will be recorded for each AE: description of the event, date and time of onset, date and time of resolution, severity, causal relationship to study drug, outcome, action taken with the study drug and any treatment given.

All abnormal changes from baseline in physical examination findings, vital signs will be collected, graded with regards to severity or clinical significance and assessed for causal relationship.

5.2 Physical Examinations and Medical History

5.2.1 Complete Physical Examination

The Investigator or designee will perform a complete physical examination at screening. Results will be recorded as part of the subject's Medical History. Assessments of height, weight, and vital signs will be collected as part of the sites standard of care and recorded on the subject's medical records. Assessments collected as part of standard of care, may be collected prior to the subject signing an informed consent if not conducted specifically for the purpose of this clinical trial. For subjects who are nonambulatory weight and height are not required to be collected if not possible. Any underlying medical condition will be recorded as ongoing baseline events for future assessment of adverse events or serious adverse events. Only adverse changes from this baseline condition will be considered adverse events or serious adverse events.

5.2.2 Targeted Physical Examination

A targeted physical examination, focusing on areas related to the reported AEs, will be obtained by the Investigator (or designee) during study visits when an AE or SAE are reported.
A targeted physical examination will also be performed at the final study visit, if clinically warranted by the presence of an AE.

All abnormal changes from baseline will be collected, graded with regards to severity, assessed with regards to causality and recorded in the CRF to be reported as abnormal physical examination findings. Only clinically significant abnormal findings are considered to be AEs and will be recorded in the subject's medical record and in the CRF.

5.2.3 Medical History

A medical history will be obtained at screening. Medical history will include demographic data (age, gender, race/ethnicity, etc.). In addition to general medical conditions, specific information relative to the underlying disease that resulted in severe spasticity requiring an intrathecal pump will be obtained and recorded in the CRF:

- Underlying disease resulting in spasticity, date of initial diagnosis, and prior treatments within the past 12 months.
- Date of implantation of an intrathecal pump. If more than one pump has been implanted the date of each implantation is requested.
- Date of surgical interventions for treatment spasticity.
- Other significant medical history.

5.3 Vital Signs

Vital signs will be collected on all subjects at screening, baseline and each study visit. If the screening and baseline visits are combined, vital signs will be collected as part of the sites standard of care from the subject's medical records. These data may be collected prior to the subject signing the informed consent if the assessment is part of the normal standard of care, and not specifically being conducted as part of this clinical protocol.

Sites should make every effort to collect a full set of vital signs on each subject post screening and baseline. Should the site have difficulties collecting vital signs on subjects due to their underlying disease condition or the cooperation of the subject, the site will be required to document in the subjects source records the attempts made and report on the CRF "NE" (not evaluable) for vital sign assessments that could not be obtained.

5.4 Documentation of Concomitant Medications

Details regarding the name, indication, dose, route of administration, and frequency of all prescription medications, will be documents from 30 days prior to dosing and through the first 12 months after initiation of study medication as part of this protocol.

6.0 PHARMACOKINETICS

No pharmacokinetic assessments are planned during this trial.

7.0 PHARMACODYNAMICS

No pharmacodynamic assessments are planned during this trial.

8.0 EFFICACY

No formal efficacy analysis is planned during this trial. However, the daily dose of Gablofen® (baclofen injection) used will be recorded for each patient in the trial.

9.0 STUDY VISITS

Refer to Appendix A for the Schedule of Study Procedures.

9.1 Screening

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the Informed Consent Form. Written informed consent must be provided by the potential study participant or legal guardian prior to initiation of any screening evaluations or other study-related procedures. The signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

After written informed consent is obtained, the subject will be assigned a five-digit number (SXX-XXX) and will undergo the designated screening procedures listed in Appendix A within 14 days prior to study drug administration. The Investigator, or his designee, will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 4.0.

9.2 Baseline Evaluations

Note that the Baseline and Screening evaluations may be combined at one visit. Baseline assessments that are considered standard of care (SOC) may be performed prior to consent of the subject and are not required to be repeated if conducted on the same day of enrollment. If the subject is determined to be eligible for participation in the study they will undergo baseline assessments. Baseline assessments are assessment of concomitant medications, complete physical examination, weight and vital signs. At the baseline visit, the remaining baclofen 2 mg/mL product in the SynchroMed® II Infusion Pump will be removed and replaced with the 3 mg/mL formulation. The flow rate for the SynchroMed® II Infusion Pump will be adjusted to maintain the patient's current daily dose of baclofen.

9.3 Interim Study Visits

Subjects will return to the investigational site approximately every 6 months or sooner if warranted by their daily dose of baclofen for assessments and pump refills. At each study interim visit subjects will be assessed for AEs and clinical signs or symptoms of an inflammatory granuloma. If an AE is reported, a targeted physical exam will be conducted to evaluate the severity and causality of the event (See Appendix A).

If interim visits more frequent than each 6 months are necessary due to the daily dose of baclofen, the site should contact the Medical Monitor to request a patient specific Appendix A that will specify the visit dates recommended for the study.

All visit dates are to be conducted within 7 days of the scheduled date (i.e. ±7days).

9.4 Final Visit

Subjects will return to the investigational site for the final visit after 36 months or when discontinued from the study for any reason. At the final study visit subjects will be assessed for AEs and clinical signs or symptoms of an inflammatory granuloma. If an AE is reported, a targeted physical exam will be conducted to evaluate the severity and causality of the event (See Appendix A). At the final study visit, all remaining 3 mg/mL Gablofen® (baclofen injection) will be removed from the SynchroMed® II Infusion Pump and replaced with commercial product at the discretion of the Investigator.

10.0 PREMATURE DISCONTINUATION FROM STUDY

A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the initial 12-month study period. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria before receiving first dose of study drug has been administered
- Death
- Significant safety event that does not resolve within 7 days of lowering the dose or other clinical interventions.
- Lost to follow-up after every attempt has been made to contact the subject including sending a registered letter
- Subject withdraws consent

The reason for the discontinuation should be recorded on the CRF.

The Principal Investigator and the Institutional Review Board/Ethics Committee (IRB/EC) reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons.

11.0 PREMATURE DISCONTINUATION FROM STUDY DRUG

The Investigator will continue to monitor subjects who have discontinued prematurely from study drug due to an AE (serious and nonserious) until resolution or stabilization of the AE.

The Investigator must complete all applicable CRF pages for subjects who discontinue study drug prematurely. Final visit procedures (i.e., AE assessment, concomitant medications review, targeted physical exam, vital signs, and weight) should be conducted for any subject who discontinues study drug prematurely.

Subjects who prematurely discontinue study drug for any reason other than toxicity may be re-entered into the study after consultation between the Investigator and the Sponsor or the Sponsor's designee. Dosing of a subject who previously discontinued in the study is at the discretion of the Sponsor. However, subjects who drop out due to toxicity will not be replaced.

12.0 PRODUCT SPECIFICATIONS

12.1 Description

Gablofen® (baclofen injection) is provided in a single use pre-filled syringe of 60,000 mcg per 20 mL (3000 mcg/mL) for intrathecal administration only.

The drug product is manufactured under current Good Manufacturing Practices (cGMP) at Cangene BioPharma, a contract manufacturing facility that has undergone FDA inspection.

12.2 Formulation, Packaging, and Labeling

Gablofen® (baclofen injection) 3 mg/mL will be supplied in single use pre-filled syringes and contains baclofen, sodium chloride and water. Syringes will be packaged in boxes for shipment to the clinical sites.

Study drug syringes will be affixed with a single label panel containing the following information:

> Gablofen® (baclofen injection) Intrathecal
> 60,000 mcg / 20 mL (3,000 mcg/mL)
> Lot Number: XXXXXX
> Manufacturing Date: MM-DD-YYYY
> Store at Room Temperature (15-30℃)
> Caution: New Drug – Limited by U.S. Federal Law to Investigational Use
> Distributed by Mallinckrodt Brands Pharmaceutical, Inc.

12.3 Receipt, Storage and Stability of Gablofen

Gablofen® (baclofen injection) 3 mg/mL syringes will be packaged in boxes for shipment to investigational sites. Excursions permitted to 4 - 30°C (6° to 86 °F), and after receipt should be stored at 15 - 30 °C (59 °- 86°F) until use.

12.4 Preparation and Administration of Study Drug

There is no manipulation or preparation of study drug other than filling into the SynchroMed® II Infusion Pump according to the manufacturer's instructions.

12.5 Ordering and Distribution of Study Drug

Study drug may be requested by submission of a medication request form. The form may be submitted to the Sponsor or designee by facsimile or electronic mail PDF as per the instructions on the drug ordering form.

12.6 Accountability of Study Drugs

All study drug received, dispensed, and returned must be accounted for in the study drug Dispensing Log, including:

- Subject number and initials
- Date study drug was dispensed
- Quantity dispensed
- Quantity returned
- Amount wasted including drug removed from a pump during refills or pump replacement

All study drug received and dispensed by the Investigator will be inventoried and accounted for throughout the study. The study drug must be stored in a restricted area with limited access. Contents of the study drug containers must not be combined.

The Investigator must maintain an accurate, up to date Dispensing Log for all study drugs supplied by the Sponsor. Study drug dispensed for all subjects must be recorded on the Drug Accountability Form. The study drug Dispensing Log and remaining drug inventory will be reviewed during monitoring visits by the Sponsor-designated clinical monitor.

The study drug supplied for this study is for use only in subjects properly consented and enrolled into this protocol. Study drugs must be kept in a secure location physically separated from standard clinic or office drug supplies.

13.0 SAFETY MONITORING AND ADVERSE EVENTS

13.1 Adverse Events

Data regarding treatment-emergent AEs will be collected in this study. Treatment-emergent AEs are events that are not present at baseline, or if present at baseline, have worsened in severity.

The descriptions and grading scales found in the CTCAE v 4.03 will be used for AE reporting. A copy of the CTCAE v 4.03 is provided in Appendix B.

The medical monitor and contact information for this study are presented below:

Yanping Zheng	Director, Clinical Affairs, Mallinckrodt, Inc.	Office: 314-654-3583 Cell: 314-452-1227	E-mail: yanping.zheng@mallinkcrodt.com

Evaluation of Adverse Events and Adverse Drug Reactions:

Adverse events in the Case Report Form (CRF) will be classified according to the most recent FDA definitions and in a manner consistent with ICH guidelines. As such the following definitions will be used:

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the "Adverse Event" case report form only if it is associated with clinical sequelae or requires therapeutic intervention. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

The reporting period for nonserious AEs starts after the first administration of study drug on Day 1 and ends after discontinuation of study medication.

If a SAE remains unresolved after discontinuation of study medication, the subject will be followed, at the investigator's discretion, until resolution of the event. SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The investigator will assess AEs for severity, for relationship to IP, and as to whether the event meets one or more of the definitions of an SAE.

The investigator will determine the relationship of an AE to the IP and will record it on the source documents and AE CRF, using the categories of unrelated, possibly related (ie, reasonable possibility of causal relationship associated with use of IP), and probably related (ie, probably or known reason to conclude that use of IP caused the event).

In order to classify adverse events and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered on the CRF, using MedDRA. CTCAE is provided in Appendix B.

Table 13-1: Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 4.03)

CTCAE Grade	Common Term	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living (ADL).
4	Life-Threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Outcome of AE was death

For those AEs that are not described on the CTCAE v 4.03, such AEs will be graded according to the same scale as defined above.

13.2 Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death
- Is life-threatening
- Requires nonscheduled (not routine or planned) in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events

Although not a formal SAE, exposure to study drug during pregnancy, even if no AE is reported in the mother, should be reported within 24 hours as an SAE.

For subjects who are hospitalized for a scheduled procedure or observation related to failures of the pump, catheter or other device malfunctions, and where the event is not related to the study medication, the hospitalization will not be considered an SAE as part of this clinical trial unless deemed possibly related to study medication by the investigator or Medical Monitor. Please contact the Medical Monitor prior to any scheduled hospitalization, for catheter or pump related corrections, to determine if this event should be recorded as an SAE or will be considered routine standard of care.

13.2.1 Reporting Requirements for Serious Adverse Events

Initial Reporting

SAEs (based on FDA/ICH definition of an SAE) require immediate reporting to Mallinckrodt or designated representative.

For all fatal or life-threatening events, the investigator(s) or designee must report information within 24 hours to the Medical Monitor at 334-868-3111.

For all SAEs, the investigator(s) or designee must complete the SAE report form with the minimum information required by FDA and ICH and fax it to Mallinckrodt Pharmacovigilance at 314-654-5759 within 24 hours of first knowledge of the event even if the experience does not appear to be related to the study drug.

The investigator(s) or designee will receive acknowledgement of receipt of the SAE report form from Mallinckrodt.

Should the investigator(s) or designee have any difficulty in sending the SAE report, they may contact Mallinckrodt Pharmacovigilance at 1-800-778-7898 (24 hour call center) or email: globalpv@mallinckrodt.com.

If there is any doubt about whether the information constitutes an SAE, the information is to be treated as an SAE.

Follow Up Reporting

The investigator(s) or designee must complete an SAE report form for all follow-up information received and fax it to the sponsor 314-654-5759 within 24 hours of receipt of additional or updated information (eg, detailed written descriptions that include copies of relevant subject records, autopsy reports and other supporting documents). The investigator(s) or designee will receive acknowledgement of receipt for each SAE report form from Mallinckrodt.

The investigator(s) or designee is required to report immediately unexpected SAEs to the responsible IRB/IEC.

All adverse events (serious and non-serious) occurring in subjects from the time of informed consent through the completion of the follow-up telephone call will be documented as an AE in the source and in the eCRF. All fields on the AE eCRF page should be completed for each event with a full description of the event and date and time of onset and resolution. The investigator must follow up on all AEs and SAEs until the events have subsided, until values return to within the acceptable range, the investigator determines that follow-up is no longer necessary, or the subject is referred to a nonstudy physician.

The sponsor will report SAEs to the FDA and investigators according to local regulations.

Table 13–2 Reporting Requirements for Adverse Events

Reporting Requirements for Adverse Events		
Seriousness	Reporting Time	Type of Report
ALL SERIOUS	Within 24 hours	Initial report on the SAE form Appropriate eCRF
	Within 24 hours of receipt of follow-up information	Follow up/final report on the SAE form
NON-SERIOUS	Per case report form submission procedure	Appropriate eCRF

Table 13–3 Contact Information for SAE Reporting

Contact Information For SAE Reporting	
Mallinckrodt Global Pharmacovigilance:	
Office Fax:	+1-314-654-5759
24-Hour Call Center Telephone:	 +1-800-778-7898
Email:	GlobalPV@mallinckrodt.com

13.2.2 Recording of Serious Adverse Events

All SAE information must be recorded on the SAE form provided by the Sponsor. Additional follow-up information (e.g., test results, autopsy, and discharge summary) may be requested to supplement the SAE report form and can be attached as de-identified records. A copy of all initial and follow-up reports must be filed with the subject's medical records.

14.0 STATISTICAL CONSIDERATIONS

14.1 Sample Size Determination

Up to 150 subjects will be enrolled at up to fifteen (15) 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.

14.2 Analysis Data Sets

Subjects who receive at least one dose of Gablofen® (baclofen injection) 3 mg/mL will be included in the safety analyses.

Subjects that continue on therapy and complete a 12-month course of therapy will be included in the assessment for inflammatory granulomas.

14.3 Data Analyses

Data will be presented as summary statistics for each dose group and each product used. The intent-to-treat (ITT) population includes all patients who were deemed eligible, have signed the informed-consent form (ICF), have been implanted with the SynchroMed® II Programmable Pump and treated with baclofen. The evaluable (or "per protocol") population is the subset of ITT patients who were deemed eligible, signed the ICF, have been clinically evaluated for inflammatory granuloma formation through a physical examination and evaluation of the investigator.

The incidence of inflammatory granulomas, suspected granulomas, and other catheter related events will be compared by a paired two-tailed T-test between each of the treatment groups. Results will be summarized in 9-month and 12-month interim reports and included in the overall study final report at the end of 3 years.

14.4 Safety

Safety data will be presented as summary and descriptive statistics, and will be provided for actual values and change from baseline values for vital signs

The incidence and severity of AEs reported during the study and their relationship to study drug will be tabulated. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) and the CTCAE v 4.03, and will be presented by body system and preferred term.

The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class.

Safety analyses will be presented by age group (pediatric and adult) and for all subjects.

14.5 Preliminary Efficacy

Efficacy will not be assessed in this trial. However, summary statistics on the daily dose of baclofen and changes in dose of baclofen will be summarized in the clinical study report.

15.0 DATACOLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

15.1 Data Collection and Reporting

A CRF will be completed for each subject who receives at least one dose of study drug. All entries on the CRF must be supported by original source documentation (e.g., laboratory reports, medical records) maintained at the investigational site.

The Investigator will review all safety assessments (AEs, vital signs, and results from physical examinations) on an ongoing basis. The Investigator is required to review all entries on the CRF and sign at appropriate time intervals.

15.2 Study Monitoring

All aspects of the study will be monitored carefully by the Sponsor's designees with respect to current Good Clinical Practice and Standard Operating Procedures for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including CRFs, source documents, etc., for review and inspection by the clinical monitor.

All CRFs will be 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of CRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

15.3 Data Disclosure and Subject Confidentiality

Subject medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection

on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the subject, except as necessary for monitoring by the IRB, the FDA, or the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor.

16.0 PROTECTION OF HUMAN SUBJECTS

16.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the South Africa revision (1996).

16.2 Institutional Review Board/Ethics Committee

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the Informed Consent Form. The study will not be initiated until the Investigator obtains written approval of the research plan and the Informed Consent Form from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56.

17.0 REFERENCE LIST

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Appendix A. Schedule of Study Procedures

Appendix A: Schedule of Study Procedures: Screening through Single-Dosing Period

Study Procedure	Screening	Baseline[a]	Visit Schedule[b]						
			Based on 6-Month Refill[c]						
Study Day	**Day -14 to -1**	**Day -3 to 1**	**6-Month**	**9- Month**	**12-Month**	**18-Month**	**24-Month**	**30-Month**	**36-Month**
Signed informed consent	X								
Medical history	X								
Compete physical exam	X								
Targeted physical exam*		X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X
Weight[d]	X	X	X	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X				
Adverse event assessment			X	X	X	X	X	X	X
Gabolfen® 3 mg/mL administration		**X[e]**							
Clinical evaluation for Inflammatory Granulomas[f]	X		X	X	X	X	X	X	X

* A targeted physical exam is defined as a limited examination for the cause and severity of a reported adverse event to assess the need for medical intervention. A general examination is not necessary.

a. Baseline evaluations must be performed within 72 hours prior to Gablofen 3 mg/mL administration on Day 1. Baseline and Screening visit may be combined. SOC assessments performed prior to informed consent may be incorporated from the medical history into study data, if not performed exclusively for this clinical trial.

b. All study visits are ±7 days from scheduled date.

c. For subjects that require refills more frequently than every 6-months due to the daily dose of baclofen, a customized Appendix A schedule may be requested from the Medical Monitor.

d. For vital signs and weight, a best effort should be conducted to obtain these data. If obtaining these data is not possible due to subject cooperation, the effort should be documented and results recorded as "not evaluable" (NE).

e. Administration of Gablofen 3 mg/mL will start on Day 1 of the study.

f. If there are clinical signs of an inflammatory granuloma as defined in Section 3.3, the Medical Monitor should be notified and an MRI scheduled to confirm the pathology of the granuloma.

Appendix B. National Cancer Institute Common Terminology Criteria for Adverse Events

Version 4.03

Publication Date: 14 June 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

18.0 SPONSOR SIGNATURE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Lawrence A. Hill
Sponsor Signature
(on behalf of James L. Young)

22 Dec 2014
Date of Signature
(DD Month YYYY)

James L. Young
Sponsor Name (print)