CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022462Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health
Service
Food and Drug
Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: November 15, 2010

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 22-462 (Gablofen; baclofen IT; SDN 1 [March 30, 2009], SDN 8 [August 4, 2009]

The sponsor (CNS Therapeutics, Inc.) has submitted NDA 22-462 Baclofen Intrathecal Injection for treatment of severe spasticity under 505(b)(2); Lioresal (NDA-20-075) is the Reference Listed Drug (RLD). IT baclofen is formulated as a sterile solution for IT administration at concentrations of 0.05, 0.5, 2 (b) (4) mg/mL. The RLD is formulated as a sterile solution for IT administration only at concentrations of 0.05, 0.5, and 2 mg/mL.

In support of clinical development and marketing approval, the sponsor has conducted four IT studies in Beagle dog (a dose-ranging study and three 28-day continuous infusion studies). These studies have been reviewed by Dr. Thompson (*Pharmacology/Toxicology NDA Review and Evaluation NDA* (b) (4)*, D. Charles Thompson, Ph.D., 3/3/2010*). Based on his review, Dr. Thompson has concluded that the "Application is considered approvable provided CMC quality and stability standards have been met", with no post-marketing requirements.

This memo briefly discusses the primary safety concern (i.e., granuloma formation) regarding IT administration of baclofen and summarizes the nonclinical study results.

- **Formation of granulomas**

It is well established, based on data in animals and humans, that drug delivery via IT infusion may be associated with formation of granulomas at the catheter tip (Deer TR *Sem Pain Med* 2(1):21-26, 2004; Deer TR *et al*. *Pain Med* 9(4):391-395, 2008; Hassenbusch SJ *et al*. *J Pain Symptom Manage* 27(6):540-563,

2004;Miele VJ *et al*. *Eur J Pain* 10:251-261, 2006; Yaksh TL *et al*. *Pain Med* 3(4):300-312, 2002). The drug for which nonclinical and clinical evidence is the greatest is morphine sulfate, administered IT for management of chronic pain. Granulomas resulting from IT morphine in humans have been characterized microscopically as follows:

> "…the typical histology emphasized the presence of macrophages, neutrophils, and monocytes, with a necrotic center and no evidence of an infectious process." (Allen JW *et al*. *Anesthesiol* 105:581-589, 2006(a)).

These (or similar) findings have been confirmed in large animal (dog, sheep) models of IT drug delivery (Allen JW *et al.*, 2006(a); Allen JW *et al*. *Anesthesiol* 105:590-598, 2006(b); Gradert TL *et al*. *Anesthesiol* 99:188-198, 2003; Yaksh TL *et al. Anesthesiol* 99:174-187, 2003).

Since the first published report in humans (North R *et al Neurosurg* 29:778-784, 1991), a number of factors have been proposed to be involved in the formation of granulomas, including allergy to the catheter material (typically, silicone), infection (either as a result of surgery or possible contamination of the drug solution), delayed injury cased by catheter implantation, foreign-body reaction, catheter design (single vs multiple-opening), property of drug (pharmacological, immunological activity), catheter tip placement, property of the formulation (e.g., pH), presence of impurities, and dose or local concentration. Studies conducted in animal models with IT opioids and information from clinical experience suggest that IT-drug induced granulomas are not due to catheter characteristics or infections, but are likely related to drug properties and high local concentrations (Allen *et al*, 2006(a); Coffey RJ, Burchiel K *Neurosurg* 50:78-86, 2002; Deer, 2004; Deer *et al*., 2008; Miele *et al*., 2006; Yaksh *et al*., 2002).

Allen *et al*. (2006(a)) assessed the time course and the role of morphine dose and concentration in granuloma formation. In the time course study, morphine (12.5 mg/mL at 40 μL/hr; 12 mg/day) was administered by continuous IT infusion to Beagle dogs for 10 or 30-31 days; dogs treated for 10 days were either sacrificed at the end of treatment or switched to continuous saline IT until study day 45, at which time they were sacrificed. Granuloma formation was followed using serial MRI scans, and was detected as early as 3 days (in 4/6 dogs) following initiation of IT infusion, and characterized as "substantial" by 10 days in all 6 dogs tested in this manner. There was evidence of mass regression during continuous IT saline, but was less the "older" the mass. In the dose and concentration study, morphine was infused IT at concentrations of 1.5, 6.25, and 12.5 mg/mL at a fixed rate of 40 μL/hr, at a concentration of 1.5 mg/mL and a rate of 334 μL/hr, or at a concentration of 12.5 mg/mL and a rate of 10 μL/hr; in controls, vehicle (saline) was administered at a rate of 40 μL/hr. The incidences of granulomas in the various groups are summarized in the following table (taken directly from Allen *et al*., 2006 a):

Table 3. Incidence in Dogs of Granulomas Defined by Magnetic Resonance Imaging or Necropsy with up to 28 Days of Intrathecal Infusion

	12 mg/ml, 40 μl/h	6 mg/ml, 40 μl/h	1.5 mg/ml, 40 μl/h	1.5 mg/ml, 333 μl/h	12.5 mg/ml, 10 μl/h	Vehicle
Total daily dose, mg	12	6	1.5	12	3	0
Incidence of granuloma	9/9	3/4	1/6	1/4	3/5	0/6

The data indicate a clear, dose/concentration related increase in the incidence of granulomas, and a lower incidence of granulomas when the same dose (12 mg/day) is administered at a lower concentration (1.5 vs 12 mg/mL). The authors noted that granulomas tended to be of smaller size when similar concentrations (12-12.5 mg/mL) were administered at a lower rate (10 vs 40 μL/hr). The authors concluded that granuloma formation with morphine is clearly (local) concentration-related, but that the studies could not address whether or not longer infusions would result in an increase in granulomas at the lower doses/concentrations.

Yaksch *et al* (2003) reported formation of granulomas in Beagle dogs treated with continuous IT morphine. Granulomas at the catheter tip were detected in all groups treated with morphine, with incidence being generally dose/concentration related (1.5-12 mg/day; 1.56-12.5 mg/mL). Granulomas were not detected in control animals or in those receiving clonidine (an α-adrenergic agonist) alone. Formation of granulomas has also been demonstrated in sheep treated for 28 days with continuous IT morphine (Gradert *et al*., 2003). Granulomas were detected in 2/3 sheep at 12 (6.25 mg/mL) and 18 (9.38 mg/mL) mg/day, but not at 3-9 (1.56-4.69 mg/mL) mg/day or in controls.

In contrast to the studies of morphine, baclofen has not been demonstrated to induce granuloma formation in animals; however, only one published study in animals of baclofen administered by continuous IT infusion could be identified. Sabbe *et al*. (1993) administered baclofen (vehicle 1mL/24 hrs, 200 μL/mL/24 hrs, or 2000 μL/mL/24 hrs) to male Beagle dogs as a continuous IT infusion using an implantable pump. Animals were sacrificed on Day 28. Histopathology findings at the catheter tip are summarized in the following table (taken directly from Sabbe *et al*., 1993):

TABLE 1: Summary of Pathology Around the Intrathecal Catheter Tip Following 28 Days of Infusion of Saline or Baclofen[A].

Site: Finding	Treatment		
	Saline	Baclofen 200 μg/ml	Baclofen 2000 μg/ml
Catheter site:			
Fibrosis	5/10[B]	8/10	6/10
Chron. inflamm.	1/10	3/10	2/10
Dura:			
Thickening/ Fibrosis	4/10	4/10	4/10
Neovascularization	3/10	3/10	4/10
Arachnoid:			
Chron. inflammation	1/10	1/10	1/10
Spinal Cord:	Intact*	Intact**	Intact
Nerve Roots:			
Calcifications	3/10	1/10	0/10

* 1 focal compression; ** 1 central infarct
[A] For further details on pathological findings, see text
[B] Ratio presents the number of animals with positive findings/ total number of animal in group

Findings were characterized as representing "a mild chronic inflammatory reaction to the foreign body of the catheter", with "no consistent variation between treatment groups". At concentrations up to 2000 μg/mL (2 mg/mL), no granulomas were reported.

There have been reports of granulomas in patients receiving IT baclofen (Deer T *et al*. *Pain Med* 8(3):259-262, 2007; Murphy PM *et al*. *Anesth Analg* 102:848-852, 2006); however, Deer *et al*. (2008) reevaluated both published reports and concluded that "…in light of the preclinical evidence and clinical experience with ITB, the reported data and images in these cases do not add up to a diagnosis of inflammatory mass." Deer *et al*. (2008) suggested that MRI findings in one case reported by Deer *et al*. (2007), involving administration of "pharmacy-compounded baclofen at a concentration of 4,000 μg/mL", actually reflected precipitation of baclofen at the catheter tip rather than a granuloma. It is not clear how Deer *et al* (2008) dismisses the finding of Murphy *et al*. (2006). Coffey & Allen (Coffey RJ, Allen JW *Anesth Analg* 104:1600-1602, 2007) stated that the MRI images provided in the Murphy *et al*. (2006) publication were "not typical of the opioid-induced inflammatory mass lesions reported…", and that the findings may have represented drug precipitate. Coffey & Allen (2007) also noted that Murphy *et al*. (2006) provided no information on "drug concentration, pump flow rate, or whether the drug administered…was the approved, preservative-free formulation of Novartis Lioresal Intrathecal®…", and stated, "we emphasize the importance of limiting intrathecal drug delivery to drugs that are tested and approved for this route of administration." Noting that similar issues were raised

by Narouze & Mekhail (Narouze SN, Mekhail NA *Anesth Analg* 104(1):209, 2007), Cousins & Murphy (Cousins MJ, Murphy PM *Anesth Analg* 104:209-210, 2007), in response to both letters, noted that "trauma of repeated catheter implantation" was not likely a cause, as the patient had received only one previous replacement (>38 months previously), that the duration of dosing (3 years) was not too short to be associated with granuloma formation, and that a 2000 μg/mL solution of Lioresal had been used. Whether or not the cases reported by Deer *et al*. (2007) and Murphy *et al*. (2006) represent baclofen-induced granuloma is unclear.

Three drugs are currently approved for IT delivery: morphine, baclofen, and ziconotide. Of these, the drug with the most clinical experience, morphine, has clearly been demonstrated to cause granulomas at the catheter tip in humans and animals. However, research to identify exactly what drug properties may be responsible have not provided definitive answers, but the data suggest that granulomas may be associated with certain drugs, primarily when administered at high concentrations. The sponsor proposes to market IT baclofen at concentrations similar to those recommended for the RLD (Lioresal) (b) (4) .

- **Continuous IT infusion studies of baclofen in Beagle dog, conducted by the sponsor.**

Three "pivotal" 28-day continuous IT infusion studies were conducted in Beagle dog (#069-002, #069-003, and #069-004). Doses for these studies were based on findings from a dose-ranging study (#069-001). As Dr. Thompson notes, none of these studies were conducted using the clinical delivery system (SynchroMed II Programmable Implantable Infusion System). The delivery system used in each "pivotal" dog study was as follows:

- Study #069-002: syringe pump (b) (4) polyurethane catheter ((b) (4)).
- Study #069-003: syringe pump (b) (4)
- Study #069-004: syringe pump (b) (4) "tapered/sheathed catheter" (b) (4)

Histopathological examinations for all "pivotal" studies were conducted by the same Study (b) (4)

In Study #069-001, baclofen was administered at doses of 500-2500 μg/day (700-3500 μg/mL; infusion rate: 30 μL/hr) to two Beagle dogs. Each dose was administered for 7 days, with no washout period prior to increases in dose.

Although data interpretation was limited by the study design, the sponsor concluded that 2000 μg/day was a maximum "practical" dose for the pivotal studies.

In Study #069-002, baclofen was administered at a single dose level (2 mg/day), using two different concentrations (2 and 4 mg/mL) administered at different rates (0.042 and 0.022 mL/hr, respectively). The first week was a dose-escalation phase; final doses were administered for 28 days. Vehicle control animals received 0.9% saline (0.042 mL/hr). There were 4 dogs/sex/group in vehicle control and baclofen-treated groups. A "Device control" (2/sex) was added during the study; however, minimal information was provided for these animals.

There were no unscheduled deaths. Clinical signs consistent with baclofen's mechanism of action ($GABA_B$ agonist) were observed in both treated groups (e.g., hind limb motor deficit, ataxia, paralysis); the incidence of these findings tended to decrease with duration of dosing. Histopathology examination revealed pyogranulomatous inflammation at the catheter tip (ranging from minimal to severe) in all dose groups, including vehicle and device controls, suggesting a lack of a drug-related effect. However, as noted in the study report,

> "…the extremely high incidence of pyogranulomatous response (50%) in Group 1 (vehicle control) and device control animals was much higher than expected, complicating the interpretation of the gross and microscopic pathology findings possibly related to the test article."

Incidence and severity (1 = slight, 2 = minimal, 3 = mild, 4 = moderate, 5 = severe) of pyogranulomatous inflammation (characterized by "intermixed macrophages and neutrophils, often forming variably formed nodules") are summarized in the following table (numbers in parentheses represent average severity in affected animals):

LOCATION	M/F	VC	baclofen		DC
			2 mg/mL	4 mg/mL	
CT	M	1/4 (3.0)	3/4 (4.7)	4/4 (3.75)	1/2 (5.0)
	F	3/4 (4.0)*	3/4 (3.3)	4/4 (3.5)	2/2 (3.5)
caudal to CT	M	1/4 (2.0)	1/4 (2.0)	1/4 (4.0)	1/2 (3.0)
	F	2/4 (3.0)	1/4 (3.0)	1/4 (4.0)	1/2 (3.0)
cauda equine	M	0/4	0/4	0/4	0/2
	F	0/4	0/4	0/4	0/2

*in one VCF, according to the Study Pathologist, "The foreign body reaction at the catheter tip contains numerous fragments that appear to be catheter material."

In Study #069-003, the experimental design was similar to that used in Study #069-002, except for the addition of a Lioresal IT group (2/sex) and fewer Device control animals (1/sex; limited data were provided). Following a 1-week dose-escalation phase, Lioresal IT was administered at a dose (concentration) of 2 mg/day (2 mg/mL) for 28 days. Two vehicle control animals were sacrificed due

to paralysis and/or paresis (Day 29, 6) and one 4-mg/mL animal was found dead on Day 6. The death in the treated animal was attributed to infection resulting from surgery. Clinical signs primarily reflected CNS effects (hind limb motor and proprioceptive deficits), and were observed to a greater extent in the IT baclofen (sponsor's product) groups compared to control. (Hind limb proprioceptive deficit was not observed in vehicle controls.) Clinical signs tended to be less in the Lioresal groups, particularly during the dose-escalation phase; however, the smaller number of animals in the Lioresal groups made comparison difficult. Toxicokinetic data were collected, but were minimal and quite variability (particularly csf levels).

Upon histopathology examination, pyogranulomatous inflammation at the catheter tip was detected in all groups, including controls, although the 2-mg/mL IT baclofen females tended to be less affected than the other groups. According to the histopathology report, "Pyogranulomatous inflammation was diagnosed if there was a mixture of neutrophils and macrophages forming an organized mass that compressed the adjacent spinal cord." Also, "exogenous material (presumably catheter material)" was detected in "numerous animals" and "While this material was often surrounded by the inflammatory reaction at the catheter tip, there did not appear to be a correlation between the presence of the catheter material (or the amount of the material) and the severity of the inflammatory reaction at the catheter tip." The incidence and severity are summarized in the following table (VC = vehicle control, DC = device control, CT = catheter tip; severity: 1 = slight, 2 = minimal, 3 = mild, 4 = moderate, 5 = severe, numbers in parentheses represent average severity in affected animals):

LOCATION	M/F	VC	baclofen		LIORESAL	DC
			2 mg/mL	4 mg/mL		
CT	M	4/4 (3.75)	2/4 (3.5)	3/4 (3.0)	2/2 (3.0)	1/1 (5.00)
	F	2/4 (3.5)	1/4 (1.0)	3/4 (3.0)	2/2 (4.5)	1/1 (5.00)
caudal to CT	M	2/4 (3.0)	1/4 (4.0)	1/4 (3.0)	1/2 (3.0)	0/1
	F	1/4 (5.0)	1/4 (1.0)	0/4	1/2 (5.0)	0/1
cauda equina	M	1/4 (4.0)	1/4 (4.0)	0/4	0/2	0/1
	F	0/4	0/4	0/4	0/2	0/1

The average severity scores differ from those in Dr. Thompson's review (page 15) since Dr. Thompson's summary table gives the sponsor's average scores, which were calculated by dividing the total severity score per group by the total number of animals in that group, not by the number of affected animals.

The study pathologist concluded that reactions at the catheter tip were detected in all groups, including controls; and that "There were no significant lesions in the Baclofen groups that were not present in the vehicle and/or device control groups". There was no discussion in the study report regarding the impact of the high incidence of pyogranulomatous reaction on study validity. However, the sponsor noted the "high incidence" of pyogranulomatous inflammation in studies # 069-002 and #069-003, according to information provided in the Introduction and Objectives section of the study report for Study #069-004.

The sponsor seems to have conducted an investigative study (Study #000-056) to determine the cause(s) of the pervasive histopathology findings in the previous studies; however, as Dr. Thompson notes, Study #000-056 was referenced as "report pending" and was not submitted in the NDA. According to the sponsor, the results suggested the presence of leachates (b) (4) with the original infusion system. Although it was originally presumed that leachates were from the adhesive used on tubing connections, "…a bench top study [also not submitted] was conducted that determined leachates (b) (4)) were present in the infusion devices, regardless if adhesive was or was not present." Although no further investigative studies appear to have been conducted, the sponsor stated that "the infusion system was modified to exclude known potential leachate producing components", based on consultation with "leading experts in the field of intrathecal delivery…" The "modified infusion system" was used in Study #069-004.

In Study #069-004 , the experimental design was similar to that of Studies #069-002 and #069-003, except that there were 4 dogs/sex in the Lioresal group and 2/sex in the Device Control group. There were no unscheduled deaths. Clinical signs (including hind limb motor and proprioceptive deficit) were observed in all treated groups; no CNS signs were observed in vehicle control (no data were provided for Device Control animals). In females, clinical signs tended to be less in the Lioresal group, compared to the IT baclofen groups. In males, clinical signs were fairly similar among treated groups.

Regarding the histopathology examination, pyogranulomatous inflammation was observed in 1-2/sex/group (including vehicle control), except that no instance was detected in the Lioresal groups. Microscopic examination was not conducted on Device Controls, but was probably unnecessary because of the lack of findings in the Lioresal group. There was no report of precipitation at the catheter tip with either 2 (b) (4) mg/mL of IT baclofen, suggesting that IT baclofen was stable in csf in vivo. The incidence and severity of pyogranulomatous inflammation are summarized in the following table (VC = Vehicle Control, severity: 1 = slight, 2 = minimal, 3 = mild, 4 = moderate, 5 = severe, numbers in parentheses represent average severity in affected animals):

LOCATION	M/F	VC	baclofen		LIORESAL
			2 mg/mL	4 mg/mL	
CT	M	1/4 (5.0)	2/4 (4.5)	1/4 (3.0)	0/4
	F	1/4 (3.0)	1/4 (3.0)	1/4 (2.0)	0/4
catheter insertion	M	0/4	0/4	1/4 (3.0)	0/4
	F	0/4	2/4 (3.0)	0/4	0/4
cauda equina	M	0/4	0/4	0/4	0/4
	F	0/4	0/4	0/4	0/4

The study pathologist concluded that "There were no gross or microscopic lesions interpreted to be due to low (2 mg/ml) or high (4 mg/ml) concentrations of

baclofen", and that the lack of pyogranulomatous inflammation in Lioresal-treated animals was considered due to chance rather than a difference between products. However, considering the incidence of pyogranulomatous inflammation in the other groups (2 to 3 of 8 total per control or treatment), at least one occurrence of pyogranulomatous inflammation might have been expected in the 8 animals treated with Lioresal.

Of the IT studies conducted by the sponsor, only Study #069-004 should be considered pivotal. Investigative studies conducted by the sponsor identified CMC concerns that resulted in (apparently) artifactual histopathology findings in all but Study #069-004. The incidence of pyogranulomatous inflammation was similar in control and IT baclofen (at both 2 and 4 mg/mL); pyogranulomatous inflammation was not reported in any Lioresal-treated animals. Therefore, as Dr. Thompson notes, there was no evidence of greater local toxicity (i.e., granuloma formation) with the 4 mg/mL concentration of IT baclofen. However, there is some concern that pyogranulomatous inflammation (i.e., granuloma) was detected in a number of animals in Study #069-004, even though the incidences were less than in the previous 28-day studies. It is unclear what a reasonable background of pyogranulomatous inflammation would be, or if incidences of ≈25-40% (based on a total of 8 per group), as noted in all but the Lioresal-treated groups, are within expected background. According to the sponsor, an incidence of 50% (as observed in Studies #069-002 and 069-003) was "a high incidence". The study pathologist did address this to some extent in the Histopathology Report:

> "In the experience of the study pathologist (spanning dozens of intrathecal studies in multiple species including rats, dogs, monkey and sheep), the development of a pyogranulomatous lesion at the catheter tip (and occasionally at the level of the catheter insertion) is a sporadic finding that varies somewhat from study to study but does (as in this study) sometime [sic] occur in vehicle (negative) control animals."
>
> "…complications in intrathecal studies, particularly in dog, are fairly common and (when present) often involve the development of some degree of a pyogranulomatous response along the catheter track. Lesions, particularly microscopic changes, related to an administered drug would be expected to be somewhat uniform among similarly treated animals. Variations of reaction along the catheter track, if not uniform, are suspect of being secondary to an unknown variable that could include the animal's individual propensity to develop a pyogranulomatous response secondary to the presence of a foreign body (catheter), variations in catheter placement, possible infection or other contamination, etc."

Although the study pathologist did not specifically state that the incidences of pyogranulomatous inflammation in this study were consistent with expected background findings, he also did not indicate that they compromised study

interpretation. However, in the Histopathology Report for Study #069-002, the same study pathologist also did not conclude that the incidences of pyogranulomatous findings in that study compromised evaluation of potentially drug-related findings, while the study report indicated otherwise.

Another concern regarding these studies is the relatively short duration of dosing. Large animal models, particularly the dog, have been demonstrated to be more sensitive than humans to morphine-induced granuloma formation at the catheter tip. In humans, granulomas have generally been detected after >6 months of dosing, whereas in Beagle dog, onset has been reported by 3 days of dosing (Allen JW *et al. Anesthesiol* 105:581-589, 2006a). There are currently no data to address whether or not there is a similar sensitivity to baclofen-induced granulomas in animals. (b) (4)

- **Conclusions and Recommendations**

Data in both animals and humans suggest that continuous IT drug infusion may result in formation of granulomas at the catheter tip, and that drug properties and local concentrations may be important factors. Since formation of granulomas at the catheter tip can result in "potentially serious" complications, including reduced efficacy, the need for surgical intervention, and "the potential for permanent neurologic injury" (Follett KA *Anesthesiol* 99(1), 2003), it is important to assess the potential for an IT-delivered therapeutic to induce granulomas. Although emphasis is placed on formation of granulomas with IT delivery, there are other potential safety concerns (such as drug-csf incompatibility, leading to drug precipitation at the catheter tip) that also need to be thoroughly assessed.

Regarding the 0.05, 0.5 and 2 mg/mL formulations of the sponsor's IT baclofen, the CMC review team has concluded that they are "qualitatively and quantitatively identical to that of reference product, Lioresal® Injection…" (*Chemistry Review for NDA 22-462, Akm Khairuzzaman, Ph.D., 12/22/2009*). Therefore, although the nonclinical studies conducted by the sponsor are not adequate (in part due to the short duration), there is no need for additional nonclinical testing.

(b) (4)

- **Recommended labeling**

The following labeling recommendations are based on the sponsor's 12-18-09 proposed labeling (SDN 16, 12/18/09), which is based on approved labeling for the RLD (Lioresal).

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- *The sponsor's first bullet should be removed from this section.*
- (b) (4)

8. USE IN SPECIFIC POPULATIONS

[Note: the sponsor's (b) (4) should be removed from this section.]

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women, Gablofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Baclofen given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times on a mg/kg basis, or 3 times on a mg/m^2 basis, the maximum oral dose recommended for human use; this dose also caused reductions in food intake and weight gain in the dams. This abnormality was not seen in mice or rabbits.

8.2 Labor and Delivery
The effect of baclofen on labor and delivery is unknown.

8.3 Nursing Mothers
At therapeutic oral doses, baclofen is excreted in human milk. It is not known whether detectable levels of drug are present in milk of nursing mothers receiving Gablofen. Because of the potential for serious adverse reactions in nursing infants from Gablofen, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The precise mechanism of action of baclofen as a muscle relaxant and antispasticity 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.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No increase in tumors was seen in rats receiving baclofen orally for two 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.

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/s/

LOIS M FREED
11/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number:	22-462
Supp Doc Num/Type/CDER	1/Orig-1 (New NDA)/30 March 2009
Stamp Date:	8/Orig-1 (Nonclinical Info)/4 August 2009
PDUFA Date:	30 April 2010
Product:	Baclofen Intrathecal Injection
Indication:	Severe Spasticity
Applicant:	CNS Therapeutics, Inc.
Review Division:	Neurology Products, HFD-120
Reviewer:	D. Charles Thompson, R.Ph., Ph.D., D.A.B.T.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell G. Katz, M.D.
Project Manager:	Lana Y. Chen, R.Ph.

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1. Executive Summary

1.1. Recommendations

1.1.1. Approvability: Application is considered approvable provided CMC quality and stability standards have been met.

1.1.2. Additional nonclinical comments: None.

1.2. Evaluation and discussion of nonclinical findings affecting regulatory decision

1.2.1. Basis of Recommendation: Lack of meaningful difference in biological response to RLD versus proposed drug product formulation in nonclinical species under relevant conditions

1.2.2. Clinical Implication: None.

2. Drug Information

2.1. Drug:

2.1.1. Pharmacological class: Muscle relaxant and antispastic

2.1.2. CAS registry number: 1134-47-0

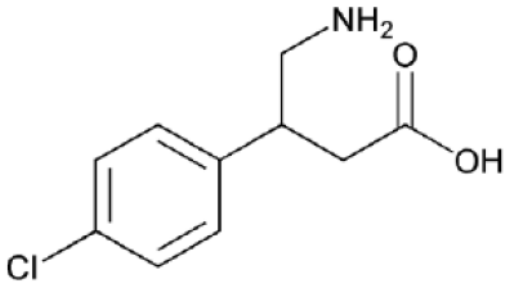
2.1.3. Generic name: Baclofen injection

2.1.4. Code name: N/A

2.1.5. Chemical name: 4-amino-3-(4-chlorophenyl) butanoic acid

2.1.6. Molecular formula/molecular weight: $C_{10}H_{12}ClNO_2$/213.66

2.1.7. Structure:



2.2. Clinical formulation:

2.2.1. Drug formulation: see sponsor's summary table reproduced below

Ingredient	0.05 mg/mL (50mcg/mL) Product Conc.	0.5 mg/mL (500mcg/mL) Product Conc.	2 mg/mL (2000mcg/mL) Product Conc.	(b) (4)
Baclofen USP				(b) (4)
Sodium Chloride USP				
Water for Injection USP				

2.2.2. Comments on excipients: No issues identified.

2.2.3. Comments on impurities/degradants: The Division has communicated to the applicant that the proposed limit of NMT (b) (4) exceeds the ICH qualification threshold and that they will need to establish that this impurity has been adequately qualified by the intrathecal route, either by demonstrating that comparable levels are present in the RLD, or by qualifying this impurity via appropriate nonclinical testing. (b) (4) This issue has subsequently been adequately addressed to the satisfaction of CMC reviewers.

2.3. Proposed clinical population and dosing regimen:

The drug product is proposed for continuous intrathecal infusion via surgically implanted infusion apparatus (pump and catheter) in patients suffering from severe spasticity (of spinal cord and cerebral origin).

Regulatory background:

Previous clinical experience:

No clinical trials have been conducted with the currently proposed clinical formulation. Rather, for this 505(b)(2) application, the applicant relies on the Agency's prior findings of safety and efficacy for the RLD, Lioresal®/baclofen intrathecal injection, which was approved on 17 June 1992 (NDA 20-075). The RLD application is owned by Medtronic, Inc., which also manufactures and distributes the SynchroMed® II delivery systems that are currently approved for chronic delivery of the drug into the intrathecal space. Currently approved Lioresal® injection product formulations contain baclofen U.S.P. at 0.05, 0.5, and 2.0 mg/mL. The applicant now proposes clinical formulations of baclofen injection at these same three concentrations (i.e., 0.05, 0.5, and 2 mg/mL) (b) (4)

(b) (4)

Relevant IND/s, NDA/s, and DMF/s:
Reference Listed Drug for this 505(b)(2) application: Lioresal/baclofen injection (NDA 20-075, approved 17 June 1992); present NDA is based on IND (b) (4).

Interaction/s w/ Agency
A pre-NDA meeting was held with the applicant on 30 April 2008 (under IND (b) (4); see appendix for relevant pharmacology/toxicology questions/responses extracted from approved meeting minutes). In addition, the applicant was informed in an NDA Filing Letter (issued 12 June 2009) of the Agency's view that "...Baclofen Intrathecal Injection [is] a combination product that consists of a drug component and a device component" and that, as a result, they would "...need to identify a specific pump, or pumps, with which your specific drug will be delivered." Nonclinical issues raised in this Filing Letter related only to the illegibility of certain portions of two of the originally submitted nonclinical study reports and a request to resubmit the noted data in a readable format. The applicant was subsequently granted a meeting with the Division (7 October 2009) to discuss the combination product issue noted above. In this meeting, the applicant was informed that "...FDA remains open to an argument that you can address our safety and efficacy concerns through labeling of your product alone" for products that are intended to be chronically infused into the intrathecal space.

3. Studies submitted within this submission:

3.1. Studies reviewed within this submission:

- 069-001: "Maximum Tolerated Dose (MTD) Toxicity Study of Baclofen Via Continuous Intrathecal Administration in Beagle Dogs"
- 069-002: "28-Day Safety Study of Baclofen Via Continuous Intrathecal Lumbar Administration in Beagle Dogs"
- 069-003: 28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs
- 069-004: 28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs

3.2. Studies not reviewed within this submission: None

3.3. Previous reviews referenced: None

4. General Toxicology

4.1. Repeat-dose toxicity

Study title: 28-Day Safety Study of Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs

Key study findings:

- Pyogranulomatous inflammation at the catheter tip was present in all groups, including the catheter controls
- Clinical/physical/neurological signs were predominantly neurological in nature (hind limb motor deficit, paresis, proprioceptive deficit, decreased activity, ataxia, recumbence, priapism, dilated pupils, and paralysis), and tended to decline in incidence with increasing duration of infusion
- Device control animals included as amendment to protocol after (~6 weeks) originally scheduled study termination

Study no.: 069-002
Study report location: Module 4, Subsection 4.2.3.2.2 (electronic submission)
Conducting laboratory and location: (b) (4)

Date of study initiation: 8 August 2008
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Intrathecal baclofen solution, 4 mg/mL (40 mL/vial), lot 2137-101, supplied by (b) (4)

Methods

Doses: See sponsor's summary table reproduced below.
Species/strain: Beagle dogs (naive to test article)
Number/sex/group: See sponsor's summary table reproduced below.
Route: Continuous intrathecal infusion
Formulation/vehicle: 0.9% saline (preservative free) vehicle; Group 3 animals received drug product formulation as supplied by manufacturer; manufacturer's drug product was diluted in vehicle at test facility for administration to Group 2 animals.
Dosing solution analyses/drug stability and homogeneity: Samples collected on 1st and last day of pump filling; samples were stored at room temperature for 1 month beyond date of terminal necropsy (13 October 2008) and then shipped at ambient temperature to (b) (4) for analysis.
Dose volume/infusion rate: See sponsor's summary table reproduced below. The applicant justifies the infusion rate parameters by noting that the Group 2 infusion/dose rate (1 mL/day; 2 mg/day) was employed by the innovator in support of registration of the RLD.

Study Design					
Study Group	Test/control Article	Concentration (mg/ml)	Infusion Rate (ml/hr)	Baclofen Dose (mg/day)	No. of Animals
1	Vehicle	0	0.042	0	4 M, 4 F
2	IT baclofen	2 mg/ml	0.042	2	4 M, 4 F
3	IT baclofen	4 mg/ml	0.022	2	4 M, 4 F
4	Device control	0	0	0	2 M, 2 F

Satellite groups used for toxicokinetics or recovery: None

Age: Approximately 1 year

Weight: Males, 11.0-13.3 kg and females, 6.6-11.5 kg

Unique study design or methodology: Animals were housed individually in stainless steel cages and were provided 400 grams of PMI Certified Canine Diet 5007 per day; water was available ad libitum. Animals were surgically implanted with a 0.9 mm OD and 0.5 mm ID fenestrated (2 fenestrations approximately 1 mm from tip) (b) (4) catheter (b) (4)) into the intrathecal space, inserted at the lumbar spine level with myelogram confirmation of catheter tip at L1/T12 level. The catheter was terminated in a subcutaneous titanium access port, into which was inserted a stainless steel L-shaped barbed needle (b) (4) and the proximal end subsequently connected to a minibore extension set (b) (4) that was stably attached to the animal. Test article administration was accomplished via connection of the minibore extension set to a syringe pump (b) (4) Justification for the infusion apparatus employed was not provided by the sponsor and the relationship to the infusion apparatus proposed for marketing cannot be established. For Study Groups 1 and 2, the syringe and pump were exchanged approximately every 2.5 days; for Group 3, only the syringe was exchanged every 5 days. Severe clinical signs observed in 3 Group 2 and 2 Group 3 animals resulted in these animals' pumps being turned off for 5-7 days and then restarted according to the dose escalation scheme outlined in the sponsor's summary table reproduced below.

NB: The study protocol calls for photographs to "...be taken of all spinal cords including the catheter tip." However, the study report states that such photographs "...were not initially obtained at necropsy or at trimming. Low power digital images were taken of all spinal cords during the microscopic examination." Neither the study protocol nor the study report contains any other description of how the catheter track was to be documented and preserved during transport between necropsy at the testing facility and the remote pathology evaluation facility. In addition, the four (2M, 2F) animals termed 'Device Control' animals were included as extra/replacement animals in the original study protocol (signed 8 August 2008) and were not added to the formal study design as 'Device Control' animals until Protocol Amendment Number 3 took effect on 25 November 2008 (~six weeks after the reported original terminal sacrifice on 13 October 2008 and at the request of the study pathologist, (b) (4)). These 'Device Control' animals were sacrificed "...at the discretion of the testing facility personnel as they were not originally scheduled for necropsy or subsequent examination"; their actual date(s) of death cannot be discerned from information provided in the study report, nor is their husbandry relative to the original study animals described.

Dose Escalation					
Study Group	Animal No.	Study Day	Dose Conc. (mg/ml)	Infusion Rate (ml/hr)	Baclofen Dose (mg/day)
2	008 (male)	1-3	2	0.004	0.192
		3-4		0.008	0.384
		4-5		0.016	0.768
		5-8		0.032	1.536
		8-36		0.042	2.0
2	019 (female)	1-3	2	0.004	0.192
		3-4		0.008	0.384
		4-5		0.016	0.768
		5-8		0.032	1.536
		8-36		0.042	2.0
2	020 (female)	1-3	2	0.004	0.192
		3-4		0.008	0.384
		4-5		0.016	0.768
		5-8		0.032	1.536
		8-36		0.042	2.0
3	009 (male)	1, 3-4*	4	0.002	0.192
		4-5		0.008	0.768
		5-8		0.016	1.536
		8-36		0.022	2.0
3	023 (female)	1-3	4	0.002	0.192
		3-4		0.004	0.384
		4-5		0.008	0.768
		5-8		0.016	1.536
		8-36		0.022	2.0

*Infusion stopped on Phase 2, Day 1 for 009 because the animal chewed through the infusion line and during the repair was inadvertently administered a bolus of 0.45 ml (1.8 mg) baclofen; infusion restarted on Day 3.

Observations times and results:

Mortality: Twice daily; all animals survived to scheduled termination.

Clinical signs: Daily; physical examinations were performed pretest, approximately every 3-5 days during dosing, and at necropsy; neurological examinations (general sensory and motor function; cerebral reflexes; spinal reflexes) were conducted pretest and at necropsy. Clinical/physical/neurological signs, primarily confined to Group 2 and 3 animals, were predominantly neurological in nature (hind limb motor deficit, paresis, proprioceptive deficit, decreased activity, ataxia, recumbence, priapism, dilated pupils, and paralysis), and tended to decline in incidence with increasing duration of infusion, even among the animals noted above whose infusions were stopped and then restarted due to initially severe clinical signs.

Body weights: Pretest and weekly on study (Groups 1-3 only); group means are summarized in the table below.

Group Mean Body Weights, kg (mean ± SD)

	Male		Females	
Group	**Day 1**	**Day 29**	**Day 1**	**Day 29**
Vehicle Control	11.8 ± 0.7	11.5 ± 0.6	7.2 ± 0.8	6.9 ± 0.9
2 mg/mL @ 1 mL/day	11.5 ± 1.3	11.1 ± 1.2	6.8 ± 0.5	6.6 ± 0.7
4 mg/mL @ 0.5 mL/day	11.1 ± 0.6	11.0 ± 0.8	7.4 ± 1.3	7.0 ± 0.8

Food consumption: Daily (Groups 1-3 only, qualitative only). No treatment-related effects were reported.
Ophthalmoscopy: Not performed.
ECG: Not performed.
Hematology: Pretest and at necropsy (except Group 4). Mean WBC (+41%) and neutrophil (+48%) values appeared to be increased, while mean RBC (-19%), Hgb (-18%), and Hct (-17%) values were decreased in Group 3 females relative to vehicle controls at necropsy. Otherwise, no treatment-related effects were reported.
Clinical chemistry: Pretest and at necropsy (except Group 4; both blood and CSF collected at necropsy). The mean serum albumin level in Group 3 females was decreased (-20%) while mean globulin was increased (+32%), resulting in a reduced A/G ratio (-37%) relative to vehicle controls at necropsy. Otherwise, no treatment-related effects were reported on serum chemistry parameters. Analyses of CSF cellular elements revealed increases in percent neutrophils (Grp2, +210%; Grp3, +186%) and decreases in percent lymphocytes (Grp2, -58%; Grp3, -53%) in females from Groups 2 and 3 versus controls. Otherwise, no treatment-related effects were reported on CSF parameters.
Urinalysis: Not performed.
Gross pathology: All animals, except those from Group 4; no treatment-related effects were reported.
Organ weights: Not collected.
Histopathology:

Adequate Battery: Yes, a standard battery of tissues was collected from all animals except those from Group 4, where only spinal cords were collected. However, only spinal cord tissue was examined microscopically from any animal.

Peer review: None

The conclusion of the study pathologist was that "Overall, there were no differences between the test article treated groups and the vehicle control or catheter control groups. Pyogranulomatous inflammation at the catheter tip was present in all groups, including the catheters controls, so this change was considered to be related to the drug delivery system, not to the test article." The incidence and severity of the pyogranulomatous lesions at the catheter tip is summarized in the sponsor's table reproduced below.

Incidence and Severity of Pyogranulomatous Lesions at the Catheter Tip

Study Group/Sex	Test/Control Article	Dose mg/day (Concentration)	Pyogranulomatous Lesion at Catheter Tip Incidence and Severity (number of animals)				
			none	minimal	mild	moderate	severe
1/M	Vehicle	0 (0 mg/mL)	3		1		
1/F	Vehicle	0 (0 mg/mL)	1		1	1	1
2/M	IT baclofen	2 (2 mg/mL)	1			1	2
2/F	IT baclofen	2 (2 mg/mL)	1	1	1		1
3/M	IT baclofen	2 (4 mg/mL)		1	1		2
3/F	IT baclofen	2 (4 mg/mL)			2	2	
4/M	Device control	-	1				1
4/F	Device control	-		1			1

Special evaluation: Low power digital images were taken of all spinal cords during microscopic examination.
Toxicokinetics: Not performed; however, baclofen concentrations were assessed in plasma at both 24 hours post infusion initiation and at necropsy and in CSF at necropsy. Results of these analyses are summarized in the table below (1.2 ng/mL was the reported lower limit of quantitation, LLOQ).

Plasma/CSF Baclofen Concentrations (ng/mL)

Group Number/ Sex	Animal Number	Plasma 24 Hours	Plasma Terminal	CSF Terminal
Group 1/Males	1	<LLOQ*	<LLOQ	<LLOQ
	2	<LLOQ	<LLOQ	<LLOQ
	3	<LLOQ	<LLOQ	<LLOQ
	4	<LLOQ	<LLOQ	<LLOQ
Group 1/Females	13	<LLOQ	<LLOQ	<LLOQ
	14	<LLOQ	<LLOQ	<LLOQ
	15	<LLOQ	<LLOQ	<LLOQ
	16	<LLOQ	<LLOQ	<LLOQ
Group 2/Males	5	27.7	30.8	78.8
	6	27.8	33.8	5.80
	7	20.3	23.8	23.8
	8	20.9	16.2	4.03
Group 2/Females	17	23.3	40.3	56.4
	18	45.7	41.5	329
	19	56.0	56.7	9.04
	20	47.0	39.6	6.04
Group 3/Males	9	20.1	5.66	<LLOQ
	10	20.6	34.4	120
	11	20.3	23.2	<LLOQ
	12	21.4	1.41	1.46
Group 3/Females	21	45.5	41.8	100
	22	24.2	24.9	62.1
	23	35.3	39.2	4.14
	24	36.3	46.2	40.4

*LLOQ = 1.2 ng/mL

Study title: 28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs

Key study findings:

- Pyogranulomatous inflammation at the catheter tip was present in all groups, including the catheter controls.
- Clinical/physical/neurological signs were predominantly neurological in nature (hind limb motor/proprioceptive deficit, hind limb paralysis/paresis/ataxia, emesis, decreased feces, and wounds/swelling/discoloration) and tended to decline in incidence with increasing duration of infusion.
- Device control animals included as amendment to protocol at time of originally scheduled study termination.

Study no.: 069-003
Study report location: Module 4, Subsection 4.2.3.2.3 (electronic submission)
Conducting laboratory and location: (b) (4)

Date of study initiation: 12 January 2009
GLP compliance: Yes, with the exceptions of CSF cell counts and test article analyses (dosing solution, CSF, and plasma)
QA statement: Yes
Drug, lot #, and % purity: Intrathecal baclofen solution (Lot 2137-101; 4 mg/mL and 40 mL/vial); positive control article, Lioresal® IT (Lots DS0031 and DS0032A; 2 mg/mL and 20 mL/vial). The report states that forty-two vials of baclofen arrived at the test facility on 27 January 2009 with "low levels of precipitates, likely due to exposure to extremely low outside temperatures (-1°F)," but was deemed usable by the sponsor following filtration.

Methods

Doses: See sponsor's summary table reproduced below.
Species/strain: Beagle dogs
Number/sex/group: See sponsor's summary table reproduced below.
Route: Continuous intrathecal infusion

Study Design

Study Group	Number of Animals		Test/Control Article	Conc. (mg/ml)	Infusion Rate (ml/hr)	Baclofen Dose (mg/day)
	Male	Female				
1	4	4	Vehicle	0	0.042	0
2	4	4	IT Baclofen	2	0.042	2
3	4	4	IT Baclofen	4	0.022	2
4	2	2	Lioresal® IT	2	0.042	2
5	1	1	Device Control	0	0	0

Formulation/vehicle: 0.9% sodium chloride (preservative-free; Lot 68- 433-DK)

Dosing solution analyses/drug stability and homogeneity: Samples collected on 1st and last day of syringe filling; samples were stored at room temperature prior to shipment to (b) (4) for analysis. Analyses indicated that the vehicle dosing solution was not contaminated with baclofen and that the Group 2, 3, and 4 dosing solutions were within 98% of target baclofen concentrations.

Dose volume/infusion rate: See sponsor's summary table reproduced above; the noted continuous infusion rates were arrived at after a graduated ramping up period of approximately 7 days and were maintained for at least 28 consecutive days

Satellite groups used for toxicokinetics or recovery: none

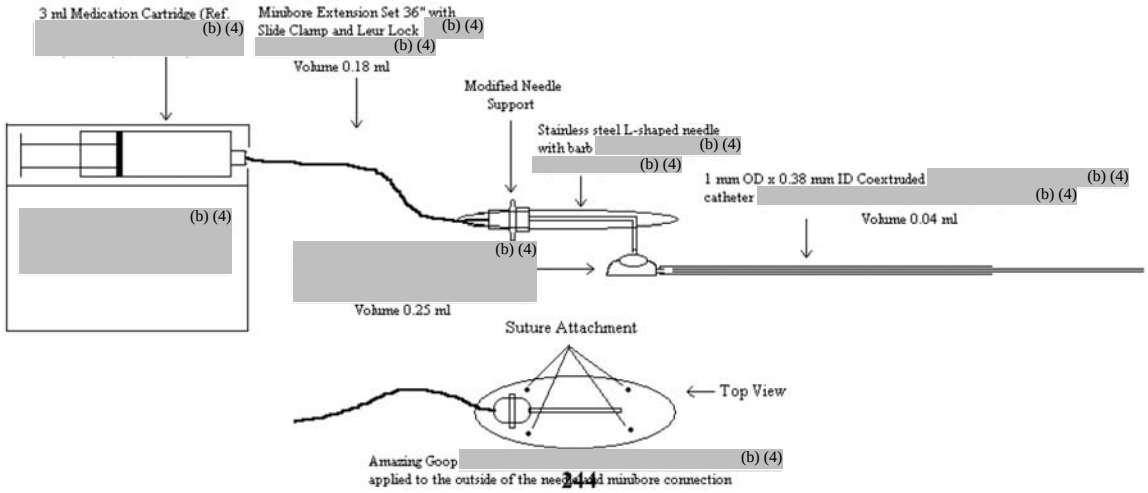
Age: Approximately 9 months

Weight: 10.7-12.2 kg (males); 7.6-9.4 kg (females)

Unique study design or methodology: Animals were housed individually in stainless steel cages and were provided 400 grams of PMI Certified Canine Diet 5007 per day; water was available ad libitum. Animals were surgically implanted with a 1.0 mm OD and 0.38 mm ID coextruded (b) (4) catheter (b) (4) inserted into the intrathecal space at the lumbar spine level with the distal tip of the catheter at the thoraco-lumbar junction as confirmed by myelogram. The proximal end of the catheter terminated in a (b) (4) Dosing administration was accomplished via an external syringe pump (b) (4) attached to a minibore extension set (see diagrammatic reproduced below from the sponsor's submission). Justification for the infusion apparatus employed was not provided by the sponsor and the relationship to the infusion apparatus proposed for marketing cannot be established. The study apparatus was changed approximately every 2.5 days for Groups 1, 2 and 4 and every 5 days for Group 3 during the 28-day continuous infusion; typically, a new syringe with a new pump was used for all groups. To achieve this, the pump was stopped, disconnected at the syringe/minibore connection and the minibore was aseptically transferred to the new pump and restarted in order to avoid administering a bolus dose to the animal.

NB: The two (1M, 1F) animals termed 'Device Control' animals were included as extra/replacement animals in the original study protocol (signed 13 January 2009) and were not added to the formal study design as 'Device Control' animals until Protocol Amendment Number 2 took effect on 4 March 2009 (i.e., during the originally scheduled terminal sacrifice time period). These 'Device Control' animals were not originally scheduled for necropsy or subsequent examination. Based on insufficient and inconclusive information provided in the study report, neither their actual date(s) of death nor their husbandry relative to the original study animals can be confirmed.

Dosing Apparatus For Continuous Infusion with an External Ambulatory Pump



Observations times and results:

Mortality: At least twice daily. Three animals were either found dead or sacrificed prematurely, as summarized in the sponsor's table reproduced below. The pathology report findings on the animal found dead (010) are reproduced below:

> This animal died as a result of subacute (being of several days duration), mixed (composed of neutrophils and lymphocytes, although neutrophils were the predominant inflammatory cell) meningitis. The severity of the meningitis and the character of the meningitis were unique to this animal in this study. The timing of the death of this animal and the neutrophilic meningitis strongly suggested the death was related to infection that may have occurred at the time of catheter placement or infection that was related to the presence of the drug delivery device.

Group	Animal Number	Sex	Necropsy		
			Date	Study Day	Reason
1	016	F	02/25/09	29	Paralysis and Paresis
1	017	F	02/02/09	6	Paresis
3	010	M	02/01/09	6	Found Dead

Clinical signs: Daily (except that no data are reported for Group 5 animals); physical examinations were performed pretest, approximately every 3-5 days during dosing, and at necropsy; neurological examinations (general sensory and motor function; cerebral reflexes; spinal reflexes) were conducted pretest and at necropsy. A summary of the incidence of selected clinical observations (number of occurrences/number of positive animals; - = not observed) is provided in the table below (Week 1 = dose escalation phase); other notable observations that were reported more sporadically with lesser incidence included hind limb paralysis/paresis/ataxia, emesis, decreased feces, and wounds/swelling/ discoloration. Physical examination findings revealed no treatment-related effects on heart rate, respiratory rate, or body temperature among males or females and

were otherwise consistent with the reported clinical observations. Neurological examination findings at necropsy revealed deficits in hind limb reflexes and/or function in males in Groups 2 and 3 only; deficits were reported in Groups 2, 3, and 4 among females.

		Group 1		Group 2		Group 3		Group 4	
Clinical Sign	**Study Week**	**Male (n = 4)**	**Female (n = 4)**	**Male (n = 4)**	**Female (n = 4)**	**Male (n = 4)**	**Female (n = 4)**	**Male (n = 2)**	**Female (n = 2)**
Motor deficit (hind limbs)	1	-	-	11/4	9/4	11/3	17/4	-	2/1
	2	2/1	5/1	22/4	27/4	17/3	24/4	-	5/1
	3	3/1	6/1	27/4	21/4	8/2	18/3	3/1	4/2
	4	5/1	8/2	13/2	8/2	8/2	12/2	5/1	3/1
	5	7/2	6/1	18/3	14/4	12/2	13/3	7/1	1/1
	6	1/1	1/1	4/3	3/2	2/2	2/1	1/1	-
Proprioceptive deficit (hind limbs)	1	-	-	10/4	2/2	6/2	7/2	-	-
	2	-	-	18/3	16/3	5/1	11/2	-	2/1
	3	-	-	4/3	4/2	-	1/1	1/1	-
	4	-	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-	6/1
	6	-	-	-	-	1/1	-	-	1/1

Body weights: Weekly (excluding Group 5 animals). Group mean body weights declined from Week 1 to Week 5 among males across all groups, ranging from -5.3% (Group 1) to -11.6% (Group 4); among females, Group 1 mean weight was essentially unchanged compared to decreases of as much as -7.4% (Group 2) in the treated groups.
Food consumption: Daily (non-quantitative) (excluding Group 5 animals); no treatment-related effects were reported.
Ophthalmoscopy: Not performed
ECG: Not performed
Hematology: Pretest and at necropsy; no treatment-related effects were reported.
Clinical chemistry: Pretest and at necropsy (CSF and blood); no treatment-related effects were reported in serum chemistry or CSF parameters.
Urinalysis: Not performed
Gross pathology: Day 35-37 for all surviving animals, plus all found dead animals; lesions at the catheter tip were common and present in all groups, including vehicle and device control groups, and were typically characterized as a darkened or discolored (tan, black) area.
Organ weights: Not performed
Histopathology:

Adequate Battery: Yes, a standard battery of tissues was collected from all animals; however, only spinal cord tissue (embedded in paraffin and stained with H&E) was examined microscopically from any animal.

Peer review: None
Special evaluation: The study protocol indicates that photographs were to be taken at necropsy (conducted at the test facility) of all spinal cords, including the

catheter tip, while gross lesions would be photographed at the discretion of the Study Director. The study pathologist's report indicates that such photographs were taken at the test facility, but they are not included or discussed further in the study report. The only images that are included are representative gross and microscopic images of the spinal cord at the level of the catheter tip that were prepared by the remote study pathologist post necropsy. The conclusions of the study pathologist are reproduced below directly from the sponsor's submission, followed by a tabular summary of microscopic findings relative to pyogranulomatous inflammation along the catheter track (CT).

> Reactions at the catheter tip were present in all groups, including the vehicle and device control groups. In all groups except the 2 mg/day Baclofen females, there were one or more animals with moderate to severe inflammation and fibrosis (with spinal cord compression) at the catheter tip. In the 2 mg/day Baclofen females, inflammation was not graded as being greater than mild.
>
> In at least one animal in all groups (except the 2 mg/day Baclofen females), including the vehicle and device control groups, there were mass-like lesions characterized as pyogranulomatous inflammation at the catheter tip. Pyogranulomatous inflammation was diagnosed if there was a mixture of neutrophils and macrophages forming an organized mass that compressed the adjacent spinal cord.
>
> There were no significant lesions in the Baclofen groups that were not present in the vehicle and/or device control groups.

Summary of Microscopic Findings: Pyogranulomatous Inflammation (CT)*

		Group 1		Group 2		Group 3		Group 4		Group 5	
Spinal Cord Section	**Sex**	**Inc**	**Avg Severity**	**Inc**	**Avg Severity**	**Inc**	**Avg Severity**	**Inc**	**Avg Severity**	**Inc**	**Avg Severity**
Catheter Tip	M	4/4	3.75	2/4	1.75	3/4	2.25	2/2	3.00	1/1	5.00
	F	2/4	1.75	1/4	0.25	3/4	2.25	2/2	4.50	1/1	5.00
Caudal to Cath Tip	M	2/4	1.50	1/4	1.00	1/4	0.75	1/2	1.50	-	-
	F	1/4	1.25	1/4	0.25	-	-	1/2	2.50	-	-
Cauda Equina	M	1/4	1.00	1/4	1.00	-	-	-	-	-	-
	F	-	-	-	-	-	-	-	-	-	-

* Inc = incidence; - = not observed; Average severity = 5.00 maximum

Toxicokinetics: Adequate sampling for kinetic analysis not performed; however, baclofen concentrations were assessed in plasma at pretest, 24 hours post infusion initiation, and at necropsy; baclofen concentrations were also assessed in CSF samples collected pretest (i.e., at surgical catheter implantation) and at necropsy. Results of these analyses are summarized in the table below (1.27 ng/mL was the reported lower limit of quantitation, LLOQ).

Plasma/CSF Baclofen Concentrations (ng/mL)

Group Number/ Sex	Animal Number	Plasma 24 Hours	Plasma Terminal	CSF Terminal
Group 1/Males	1	<LLOQ*	<LLOQ	<LLOQ
	2	<LLOQ	<LLOQ	<LLOQ
	3	<LLOQ	<LLOQ	<LLOQ
	4	<LLOQ	<LLOQ	<LLOQ
Group 1/Females	15	<LLOQ	<LLOQ	<LLOQ
	16	<LLOQ	<LLOQ	<LLOQ
	17A	<LLOQ	<LLOQ	<LLOQ
	18	<LLOQ	<LLOQ	<LLOQ
Group 2/Males	5	19.6	14.8	304
	6	23.9	30.1	93.3
	7	29.9	35.7	135
	8	18.4	20.3	4.42
Group 2/Females	19	28.7	38.6	520
	20	31.2	46.4	111
	21	44.7	36.2	138
	22	39.0	<LLOQ	2.30
Group 3/Males	9	23.2	31.9	310
	10A	18.4	28.2	12.1
	11	20.5	18.5	12.7
	12	27.2	28.4	158
Group 3/Females	23	26.4	22.9	117
	24	43.8	37.7	69.7
	25	30.4	<LLOQ	<LLOQ
	26	34.6	33.2	42.4
Group 4/Males	13	21.6	1.34	<LLOQ
	14	20.1	26.9	1310**
Group 4/Females	27	42.4	29.7	11.1
	28	28.3	33.6	43.4

*LLOQ = 1.27 ng/mL
**Sample diluted 50% to fit within calibration range

Study title: 28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs

Key study findings:

- There was no meaningful difference in spinal cord histopathological lesions observed between animals exposed to vehicle and those exposed to any tested baclofen formulation. The spinal cord lesions observed appeared to be due largely to the placement and/or presence of the intrathecal catheter.
- Spinal cord tissue specimens from Group 5 (device control) animals were not examined microscopically.

Study no.: 069-004
Study report location: Amendment 0006 (electronic submission, 31 July 2009)
Conducting laboratory and location: (b) (4)

Date of study initiation: 14 May 2009

GLP compliance: Yes, with the exceptions as described in the compliance statement reproduced below from the sponsor's submission

> CSF cell counts and CSF cultures performed by (b) (4) and the CSF, plasma, and dosing solution samples analyzed for test article concentration by (b) (4), were not conducted under GLP Guidelines, but were performed in accordance with the protocol, protocol amendments, and their SOPs. Portions of the study performed by (b) (4) were conducted according to the protocol, protocol amendments, the aforementioned GLPs, and to each contributor's SOPs. The compliance status of the portions of this study performed at (b) (4) was the responsibility of the respective groups. The NBR Quality Assurance Statement is included with this report. Quality Assurance Statements from each outside laboratory is included with the appropriate appendix. The study was conducted in accordance with the protocol and protocol amendments as approved by the Sponsor (Appendix A).

QA statement: Yes

Drug, lot #, and % purity: Intrathecal baclofen solution (lot 2133-101; 4 mg/mL and 20 mL/vial); positive control article, Lioresal® IT (lot DS0034; 2 mg/mL and 20 mL/vial).

Methods

Doses: See sponsor's summary table reproduced below.

Species/strain: Beagle dogs

Number/sex/group: See sponsor's summary table reproduced below.

Route: Continuous intrathecal infusion

Study Design

Study Group	Number of Animals		Test/Control Article	Conc. (mg/ml)	Infusion Rate (ml/hr)	Baclofen Dose (mg/day)
	Male	Female				
1	4	4	Vehicle	0	0.042	0
2	4	4	IT Baclofen	2	0.042	2
3	4	4	IT Baclofen	4	0.022	2
4	4	4	Lioresal® IT	2	0.042	2
5	2	2	Device Control	0	0	0

Formulation/vehicle: 0.9% sodium chloride (preservative-free; lot 71-160-DK)

Dosing solution analyses/drug stability and homogeneity: Samples collected on 1st and last day of dosing; samples were stored at room temperature prior to shipment to (b) (4) for analysis. Analyses indicated that the vehicle dosing solution was not contaminated with baclofen and that the Group 2, 3, and 4 dosing solutions were within ±5% of target baclofen concentrations.

Dose volume/infusion rate: See sponsor's summary table reproduced above; the noted continuous infusion rates were arrived at after a graduated ramping up period of approximately 7 days and were maintained for at least 28 consecutive days

Satellite groups used for toxicokinetics or recovery: none

Age: Approximately 10 months

Weight: 9.6-12.7 kg (males); 7.8-10.1 kg (females)

Unique study design or methodology (if any): Animals were housed individually in stainless steel cages and were provided 400 grams of PMI Certified Canine Diet 5007 per day; water was available ad libitum. Animals were surgically implanted at the level of L4-L6 with a fenestrated, tapered/sheathed catheter (0.9 mm OD and 0.5 mm ID, (b) (4) into the intrathecal space. The catheter was secured with acrylic and the proximal end connected to the pump catheter (1.15 mm OD and 0.8 mm ID, PE 100) with a stainless steel connector. The pump catheter was tunneled anterior to the incision, passed through the skin via a small stab incision and connected to the reservoir of the infusion pump. Catheter placement was confirmed via myelogram. Dosing administration was accomplished via an external syringe pump (b) (4) attached to the externalized (b) (4) tubing with a blunt needle. The study apparatus was changed one time during the dose escalation and approximately every 2.5 days for Groups 1, 2 and 4 and every 5 days for Group 3 during the 28/29-day continuous infusion. Typically, a new syringe with a new pump was used for all groups. To achieve this, the pump was stopped, disconnected at the syringe/blunt needle connection and the blunt needle was aseptically transferred to the new pump and restarted. Justification provided by the sponsor for the infusion apparatus employed is reproduced below in its entirety; no explanation is provided for how the tested apparatus is expected to provide support for the infusion apparatus proposed for marketing.

> In previous studies with baclofen (NBR Studies 069-002 and 069-003) [reviewed above] pyogranulomatous inflammation was present in all groups, including vehicle control and untreated device controls, at a high incidence (~50%). The lesions were not baclofen related and were believed caused by leachates from the infusion device. Subsequently, a study was conducted (b) (4) [A report of this study is described by the sponsor as "pending" and has not been submitted.] that tested infusion devices that did not have adhesive on the tubing connections. Animals tested with the adhesive free infusion devices did not develop pyogranulomatous inflammatory lesions. Concurrently a bench top study was conducted that determined leachates (b) (4) were present in the infusion devices, regardless if adhesive was or was not present. After review of the results of the studies, and consultation with leading experts in the field of intrathecal delivery including Dr. Tony Yaksh, the infusion system was modified to exclude known potential leachate producing components. The present study was conducted with the modified infusion system.

Observations times and results:

Mortality: Twice daily. All animals survived to scheduled necropsy.

Clinical signs: Daily (except that no data are reported for Group 5 animals); physical examinations were performed pretest, approximately every 3-5 days during dosing, and at necropsy; neurological examinations (general sensory and motor function; cerebral reflexes; spinal reflexes) were conducted pretest and at necropsy. A summary of the incidence of selected clinical observations (number of occurrences/number of positive animals; - = not observed) is provided in the table below (Week 1 = dose escalation phase); other notable observations that were reported more sporadically with lesser incidence included hind limb paralysis/paresis, excessive salivation, and wounds/swelling/discoloration. Physical examination findings revealed no treatment-related effects on heart rate, respiratory rate, or body temperature among males or females and were otherwise consistent with the reported clinical observations. Neurological examination findings at necropsy revealed deficits in hind limb spinal reflexes and/or motor function in males in Groups 2, 3, and 4; among females, deficits in hind limb motor function were detected only in 2/4 Group 3 animals, while deficits in hind limb spinal reflexes were evident in animals from Groups 2, 3, and 4.

		Group 1		Group 2		Group 3		Group 4	
Clinical Sign	**Study Week**	**Male (n = 4)**	**Female (n = 4)**	**Male (n = 4)**	**Female (n = 4)**	**Male (n = 4)**	**Female (n = 4)**	**Male (n = 4)**	**Female (n = 4)**
Motor deficit (hind limbs)	1	-	-	19/4	17/4	16/4	15/4	20/4	4/1
	2	-	-	25/4	22/4	28/4	28/4	28/4	9/2
	3	-	-	19/3	21/3	26/4	23/4	28/4	7/1
	4	-	-	14/3	16/4	23/4	27/4	28/4	7/1
	5	-	-	15/3	3/2	18/3	18/4	19/4	7/1
	6	-	-	3/2	1/1	6/2	5/3	6/4	2/1
Proprioceptive deficit (hind limbs)	1	-	-	12/4	12/4	14/4	11/4	19/4	4/1
	2	-	-	18/3	12/3	21/4	24/4	21/4	8/2
	3	-	-	4/2	6/2	11/3	13/4	16/3	3/1
	4	-	-	1/1	2/1	3/2	11/3	10/3	5/1
	5	-	-	3/2	-	1/1	9/2	7/1	6/1
	6	-	-	-	1/1	1/1	2/2	2/1	1/1
Emesis	1	-	-	6/2	4/2	7/3	7/3	1/1	2/2
	2	-	-	4/2	3/2	6/4	3/2	5/2	1/1
	3	-	-	3/1	1/1	2/2	2/2	2/1	1/1
	4	-	-	-	1/1	1/1	1/1	1/1	-
	5	-	-	1/1	1/1	5/2	3/3	5/2	-
	6	-	-	-	-	2/2	-	-	-
Decreased feces/ mucoid feces	1	1/1	-	-	5/3	1/1	6/2	1/1	1/1
	2	-	-	7/3	1/1	5/2	7/4	4/3	-
	3	-	-	1/1	1/1	3/2	1/1	1/1	1/1
	4	-	-	-	-	1/1	-	1/1	-
	5	-	-	1/1	-	-	3/2	2/1	1/1
	6	-	-	-	-	-	1/1	-	-

Body weights: Weekly (excluding Group 5 animals). Mean body weights from Day 1 to Week 5 declined in males of Groups 2, 3, and 4 from -12.1% to -12.5%, versus -4.8% in vehicle-treated controls; among females, percentage decreases were -4.4%, -8.1%, -10.1%, and -5.5% in Groups 1, 2, 3, and 4, respectively.
Food consumption: Daily (non-quantitative) (excluding Group 5 animals). No treatment-related effects were reported.
Ophthalmoscopy: Not performed.
ECG: Not performed.
Hematology: Pretest and at necropsy; no treatment-related effects were reported.
Clinical chemistry: Pretest and at necropsy (CSF and blood); no treatment-related effects were reported in serum chemistry or CSF parameters.
Urinalysis: Not performed.
Gross pathology: Days 36-39 on all animals. No treatment-related effects were reported.
Organ weights: Not performed
Histopathology:

Adequate Battery: Yes, a standard battery of tissues was collected from all animals; however, only spinal cord tissue (embedded in paraffin and stained with H&E) was examined microscopically from any animal (tissues from Group 5 animals were excluded from microscopic analysis).

Peer review: None

Special evaluation: The study protocol indicates that photographs were to be taken at necropsy (conducted at the test facility) of all spinal cords, including the catheter tip, while gross lesions would be photographed at the discretion of the Study Director. Photographs of trimmed and untrimmed spinal cords for all study animals in Groups 1 through 4 are appended for reference to the study pathologist's report.

The conclusions of the study pathologist are reproduced below directly from the sponsor's submission, followed by the study pathologist's tabular summary of microscopic findings from analysis of spinal cord tissue at the level of the catheter tip.

> There were no gross or microscopic lesions interpreted to be due to low (2 mg/ml) or high (4 mg/ml) concentrations of baclofen.
>
> Most if not all the lesions noted during the gross and microscopic assessments of the spinal cord from the study animals were due to the placement and/or presence of the intrathecal catheter.
>
> The highest concentration of the test article (4 mg/ml of baclofen) did not cause catheter track inflammation (including pyogranulomatous inflammation) at an incidence or average severity that was above the level of the vehicle controls or above the levels noted in the 2 mg/ml dose group. The lower concentration of baclofen (2 mg/ml) was associated with catheter track inflammation (including pyogranulomatous inflammation) at about the same incidence and average severity as controls. Any differences in gross or microscopic changes between all three groups (vehicle control, 2 mg/ml baclofen and 4 mg/ml baclofen) were likely due to factors associated with

the placement and/or presence of the intrathecal catheter or due to chance resulting from biologic variation.

Administration of the test article (baclofen), via an intrathecal catheter and under the other conditions defined in the study protocol, at a concentration/flow rate of 2 mg/ml/0.042 ml/hr and 4 mg/ml/0.022 ml/hr were not associated with any adverse effects in the spinal cord or surrounding tissues except those changes interpreted to be due to the placement and/or presence of the intrathecal catheter (i.e. changes also present in vehicle controls).

STUDY ID: 069-004		Microscopic Evaluation Data																																					
Group Title		GROUP 1								Summary Data GROUP 1		GROUP 2								Summary Data GROUP 2		GROUP 3								Summary Data GROUP 3		GROUP 4								Summary Data GROUP 4	
Group Dose		VEHICLE								Gp Size=	8	IT BACLOFEN 2 mg/ml; 0.042 mlhr								Gp Size=	8	IT BACLOFEN 4 mg/ml; 0.022 mlhr								Gp Size=	8	LIORESAL IT 2 mg/ml; 0.042 mlhr								Gp Size=	8
		Animals										Animals										Animals										Animals									
Fate		SS	SS	SS	SS	SS	SS	SS	SS			SS	SS	SS	SS	SS	SS	SS	SS			SS	SS	SS	SS	SS	SS	SS	SS			SS	SS	SS	SS	SS	SS	SS	SS		
Days on Test		36	36	37	37	36	36	37	37			36	36	37	37	36	36	37	37			36	39	37	37	36	36	37	37			36	36	37	37	36	36	37	37		
Sex		M	M	M	M	F	F	F	F			M	M	M	M	F	F	F	F			M	M	M	M	F	F	F	F			M	M	M	M	F	F	F	F		
TISSUE	DIAGNOSIS	001	002	003	004	019	020	021	022	INC	AVG SEV	005	006	007	008	023	024	025	026	INC	AVG SEV	009	010	011	012	027	028	029	030	INC	AVG SEV	013	014	015	016	031	032	033	034	INC	AVG SEV
SPINAL CORD - CATHETER TIP	EXAMINED	Y	Y	Y	Y	Y	Y	Y	Y	8		Y	Y	Y	Y	Y	Y	Y	Y	8		Y	Y	Y	Y	Y	Y	Y	Y	8		Y	Y	Y	Y	Y	Y	Y	Y	8	
-	NORMAL	-	-	-	-	-	-	-	-	0		-	-	-	-	-	-	-	-	0		-	-	-	-	-	-	-	-	0		-	-	-	-	-	-	-	-	0	
-	MENINGES, INFILTRATES	1	-	-	-	-	-	-	-	1	0.13	-	-	-	-	3	-	-	-	1	0.38	1	-	-	-	3	-	-	-	2	0.50	-	-	-	-	-	-	1	-	1	0.13
-	MENINGES, INFILTRATES % MONONUCLEAR CELLS	100	-	-	-	-	-	-	-	-	-	-	-	-	-	100	-	-	-	-	-	50	-	-	-	100	-	-	-	-	-	-	-	-	-	-	-	100	-	-	-
-	MENINGES, INFILTRATES % GRANULOCYTES	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-	CT, PRESENT	P	P	P	P	P	P	P	P	8	0.00	P	P	P	P	P	P	P	P	8	0.00	P	P	P	P	P	P	P	P	8	0.00	P	P	P	P	P	P	P	P	8	0.00
-	CT, FIBROSIS	1	1	2	3	2	1	3	1	8	1.75	1	-	1	2	2	1	1	2	7	1.25	2	2	1	1	2	1	2	2	8	1.63	2	1	1	1	1	1	1	2	8	1.25
-	CT, COMPRESSION	2	1	1	4	3	2	2	2	8	2.13	2	4	1	3	3	1	-	1	7	1.88	1	1	-	2	1	-	2	2	6	1.13	2	1	-	-	2	-	2	1	5	1.00
-	CT, SC, PENETRATION	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00	-	-	-	P	-	-	-	-	1	0.00
-	CT, INFLAMMATION	2	-	1	5	4	1	2	1	7	2.00	-	5	-	4	4	-	-	1	4	1.75	2	-	-	3	3	1	-	2	5	1.38	2	1	-	-	-	-	1	2	4	0.75
-	CT, INFLAMMATION, MONONUCLEAR CELLS (%)	80	-	90	50	20	100	50	100	-	-	-	50	-	50	50	-	-	100	-	-	70	-	-	50	50	30	-	100	-	-	70	100	-	-	-	-	100	100	-	-
-	CT, INFLAMMATION, GRANULOCYTES (%)	20	-	10	50	80	-	50	-	-	-	-	50	-	50	50	-	-	-	-	-	30	-	-	50	50	70	-	-	-	-	30	-	-	-	-	-	-	90	-	-
-	CT, INFLAMMATION, PYOGRANULOMATOUS	-	-	-	5	3	-	-	-	2	1.00	-	5	-	4	3	-	-	-	3	1.50	-	-	-	3	2	-	-	-	2	0.63	-	-	-	-	-	-	-	-	0	0.00
-	CT, EXOGENOUS MATERIAL	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	P	-	-	-	1	0.00	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00
-	SPINAL CORD, PERIVASCULAR INFILTRATES	-	-	-	4	1	-	-	-	2	0.63	-	4	-	-	2	-	-	-	2	0.75	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	2	-	1	0.25
-	DORSAL TRACTS, NERVE FIBER DEGENERATION	-	-	2	4	2	2	3	1	6	1.75	3	2	-	-	1	-	1	1	5	1.00	1	1	-	3	1	-	-	1	5	0.88	1	-	-	2	-	-	-	-	2	0.38
-	LATERAL TRACTS, NERVE FIBER DEGENERATION	-	-	-	-	-	-	-	-	0	0.00	2	4	-	-	-	-	-	-	2	0.75	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00
-	VENTRAL TRACTS, NERVE FIBER DEGENERATION	-	-	-	-	-	-	-	-	0	0.00	-	4	-	-	-	-	-	-	1	0.50	-	-	-	-	-	-	-	-	0	0.00	-	-	-	3	-	-	-	-	1	0.38
-	EPIDURAL SOFT TISSUE, INFLAMMATION	-	-	-	-	-	-	-	-	0	0.00	-	3	-	-	3	-	-	-	2	0.75	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00
-	SC, GRAY MATTER, AXON SPHEROIDS	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00	-	1	-	-	-	-	-	-	1	0.13	-	-	-	-	-	-	-	-	0	0.00
-	SPINAL CORD NECROSIS	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00	-	-	-	-	-	-	-	-	0	0.00	-	-	-	1	-	-	-	-	1	0.13

Toxicokinetics: Adequate sampling for kinetic analysis not performed; however, baclofen concentrations were assessed in plasma at pretest, 24 hours post infusion initiation, and at necropsy; baclofen concentrations were also assessed in CSF samples collected pretest (i.e., at surgical catheter implantation) and at necropsy. Results of these analyses are summarized in the table below (1.24 ng/mL was the reported lower limit of quantitation, LLOQ).

Plasma/CSF Baclofen Concentrations (ng/mL)

Group Number/ Sex	**Animal Number**	**Plasma 24 Hours**	**Plasma Terminal**	**CSF Terminal**
Group 1/Males	1	<LLOQ*	<LLOQ	<LLOQ
	2	<LLOQ	<LLOQ	<LLOQ
	3	<LLOQ	<LLOQ	<LLOQ
	4	<LLOQ	<LLOQ	<LLOQ
Group 1/Females	19	<LLOQ	<LLOQ	<LLOQ
	20	<LLOQ	<LLOQ	<LLOQ
	21	<LLOQ	<LLOQ	<LLOQ
	22	<LLOQ	<LLOQ	<LLOQ
Group 2/Males	5	36.6	25.3	393
	6	52.5	46.8	1.75
	7	32.3	25.4	103
	8	46.5	36.0	56.5
Group 2/Females	23	45.6	19.6	173
	24	55.1	51.1	1080**
	25	58.5	44.8	97.5
	26	98.6	64.5	594**
Group 3/Males	9	56.6	44.6	358
	10	67.9	38.9	478
	11	48.5	44.2	373
	12	61.9	32.5	653
Group 3/Females	27	61.3	44.6	216
	28	60.7	63.6	33.5
	29	54.6	41.2	394
	30	42.5	43.0	730
Group 4/Males	13	42.6	32.3	1010
	14	32.5	23.3	873
	15	50.9	35.2	1180
	16	38.5	40.0	240
Group 4/Females	27	61.3	44.6	216
	28	60.7	63.6	33.5
	29	54.6	41.2	394
	30	42.5	43.0	730
Group 5/Males	17	<LLOQ	<LLOQ	<LLOQ
	18	<LLOQ	<LLOQ	<LLOQ
Group 5/Females	35	<LLOQ	<LLOQ	<LLOQ
	36	<LLOQ	<LLOQ	<LLOQ

*LLOQ = 1.24 ng/mL

**Sample diluted 50% and reanalyzed after initial results were outside calibration range

Study title: Maximum Tolerated Dose (MTD) Toxicity Study of Baclofen Via Continuous Intrathecal Administration in Beagle Dogs

Key study findings:

- Both animals lost weight over the course of the study (15-22%).
- Clinical effects/neurological deficits were evident at the lowest dose level (500 µg/day), but tolerance was observed with increasing dose and time.

Study no.: 069-001
Study report location: Module 4, Subsection 4.2.3.2.1 (electronic submission)
Conducting laboratory and location: (b) (4)

Date of study initiation: 9 July 2008
GLP compliance: No
QA statement: None
Drug, lot #, and % purity: baclofen injection, 4 mg/mL (batch ER 2137-7)

Methods:

Doses: see sponsor's summary table reproduced below
Species/strain: beagle dogs (naive to test article)
Number/sex/group or time point: 2 males
Route: intrathecal infusion
Formulation/vehicle: 0.9% saline (lot #58-222-DK, preservative free)
Dosing solution analyses/drug stability and homogeneity: not performed
Dose volume/infusion rate: see sponsor's summary table reproduced below
Satellite groups used for toxicokinetics or recovery: none
Age: 2-2.5 years at time of surgical catheter implant
Weight: 13.5-15.1 kg at time of surgical catheter implant
Unique study design or methodology: Animals were surgically implanted with a 0.9 mm OD and 0.5 mm ID fenestrated (2 fenestrations approximately 1 mm from tip) (b) (4) catheter (manufacturer make and model number not specified) into the intrathecal space, inserted at the lumbar spine level with myelogram confirmation of catheter tip at L1/T12 level. The catheter was terminated in a subcutaneous titanium access port, which was subsequently (on Study Day 1) connected to a (b) (4) manufacturer not specified) via a "minibore extension set and stainless steel L-shaped barbed needle" (manufacturer make and model number not specified). Animals were housed individually in stainless steel cages and were provided 400 grams of PMI Certified Canine Diet 5007 per day; water was available ad libitum.

Study Design				
Dose (µg/day)	Concentration (µg/ml)	Infusion Rate (µl/hr)	Daily Infusion Rate (ml/day)	Days of Infusion[a]
500	700	30	0.72	1-7
1000	1400	30	0.72	8-14
2000	2800	30	0.72	15-21
2500	3500	30	0.72	22-28

[a]At the first pump fill, the catheter was primed with the 700 µg/ml dosing solution. At the subsequent dose increases, the catheters were not primed and the animals did not begin receiving the higher dose until approximately 21 hours after the new dose was initiated.

Summary Results and Conclusions:
Limitations of the study design (only 2 male treated animals on study with no controls) confound substantive interpretation and conclusions based on the study findings. Evaluation consisted of assessments of body weight, food consumption, and physical/neurological appearance and function. At study termination, the two animals were subjected to gross necropsy and the spinal cords were harvested for histopathological examination.

Reported clinical signs included paresis, motor deficit, and proprioceptive deficit of the hind limbs; hind feet misplacement; recumbency; ataxia; and moist exanthema. Both animals lost weight over the course of the study (15-22%), which was consistent with periodic decreased food consumption. Neurological deficits were observed, more so in Animal 001 than 002, and more so early in the study, as tolerance to the effects of the drug was reported with increasing dose and time. Histopathological examination of the spinal cords also revealed significant differences between responses of the two animals. In Animal 001, minimal infiltrates and fibrosis were observed along the catheter track, with minimal nerve fiber degeneration evident in a single lumbar spinal nerve root. The sponsor's study pathologist interpreted these findings to be due to the presence of the catheter itself. Animal 002, in contrast, was observed to have pyogranulomatous inflammation along the catheter overlying the lumbar spinal cord, which the pathologist was unable to distinguish as having been caused by the catheter, the test article, or a combination of both. A small open skin wound lateral to the surgical incision site was noted in this animal at necropsy (Day 28), which the pathologist suggests may have resulted in bacterial infection spreading along the catheter tract. However, no bacteria were observed upon microscopic examination.

Based on the findings under the conditions of this study, the sponsor concluded that "2000 µg/day is a practical dose limit for a longer term infusion study".

5. Overall integrated summary and safety evaluation:

The current application is a 505(b)(2) NDA based on the RLD, Lioresal®/baclofen intrathecal injection, which was approved on 17 June 1992 (NDA 20-075). The drug product is proposed for continuous intrathecal infusion in the management of severe

spasticity. Currently approved Lioresal® injection product formulations contain baclofen U.S.P. at 0.05, 0.5, and 2.0 mg/mL. (b) (4)

(b) (4)

The Agency has communicated its view to the applicant that "...Baclofen Intrathecal Injection [is] a combination product that consists of a drug component and a device component" and that, as a result, the applicant would "...need to identify a specific pump, or pumps, with which your specific drug will be delivered." The RLD application is owned by Medtronic, Inc., which also manufactures and distributes the SynchroMed® II delivery systems that are currently approved for chronic delivery of the RLD into the intrathecal space.

In support of the proposed application, the applicant has submitted a report from a non-GLP dose range-finding study in dogs and reports from three separate GLP 28-day continuous intrathecal infusion studies in dogs. Based on reports in the literature of previous nonclinical/clinical experience with the RLD[1] and in consultation with the Division, it was agreed that the purpose of the intrathecal study in dog is to assess toxicity at the site of application, rather than pharmacodynamic activity, and that the primary local toxicity of concern is the development of granulomas.

The reasons stated by the applicant for conduct of three separate 28-day dog studies were that pyogranulomatous inflammation was observed in all dose groups of the first two studies, including vehicle and untreated device controls, at a high incidence (~50%) and, as a result, the infusion apparatus employed was different in each of the three studies. Specifically, the pump that was utilized (b) (4)) was an external syringe pump connected through a dermal access port to the IT-implanted catheters, which were different in each of the three studies. In the dose range-finding and initial 28-day studies, fenestrated (b) (4) catheters ((b) (4) , were employed. In the second 28-day study, a coextruded, (b) (4) catheter (b) (4) was

[1] For example, see: Sabbe MB, Grafe MR, Pfeifer BL, Mirzai TH, Yaksh TL. Toxicology of baclofen continuously infused into the spinal intrathecal space of the dog. Neurotoxicology. 1993 Winter;14(4):397-410; Deer TR, Raso LJ, Coffey RJ, Allen JW. Intrathecal baclofen and catheter tip inflammatory mass lesions (granulomas): a reevaluation of case reports and imaging findings in light of experimental, clinicopathological, and radiological evidence. Pain Med. 2008 May-Jun;9(4):391-5; Deer TR, Raso LJ, Garten TG. Inflammatory mass of an intrathecal catheter in patients receiving baclofen as a sole agent: a report of two cases and a review of the identification and treatment of the complication. Pain Med. 2007 Apr;8(3):259-62; and Murphy PM, Skouvaklis DE, Amadeo RJ, Haberman C, Brazier DH, Cousins MJ. Intrathecal catheter granuloma associated with isolated baclofen infusion. Anesth Analg. 2006 Mar;102(3):848-52.

employed. And, finally, in the third 28-day study, a fenestrated, tapered/sheathed catheter (b) (4) was employed. In each study, the pump/syringe apparatus was exchanged for a new apparatus every 2-5 days over the study duration. Importantly, the animal (dog) data submitted to date under the NDA have not been generated utilizing either the Medtronic Synchromed II pump or the Medtronic Indura IT catheter (b) (4)) that comprise the drug infusion apparatus proposed for marketing by the applicant. The applicant provides no explanation for how the tested infusion system(s) are supposed to provide safety data relevant to supporting the combination of baclofen drug product formulation and infusion system that are actually proposed for market entry.

Thus, the adequacy of the submitted nonclinical data to achieve the objective for which they were intended is, at the least, brought into question based on the noted fundamental aspects of the study designs employed, even before the first study results were examined. Other limitations of the reported studies include: 1) the dose range-finding study was inadequate based on inclusion of only two male animals and absence of any control group; 2) the dose groups and the numbers of animals in them was not uniform across the three 28-day studies, such as an RLD-dosed group being absent in the first 28-day study (069-002), present with only 2 dogs/sex in the second study (069-003), and present with 4 dogs/sex in the third study (069-004); 3) only spinal cord tissue was examined in any of the submitted studies; 4) the 28-day study duration was sub-optimal based on current state of the science for a chronic IT dog study; 5) a 'Device Control' group was only included in the first two studies as an afterthought, by protocol amendment (as much as six weeks after the original necropsy date in 069-002), while such a 'Device Control' group was included by original protocol design in the third study (069-004), but then the spinal cord tissue from these animals was not even examined microscopically; and 6) adequate sampling to conduct a thorough kinetic analysis of baclofen levels in CSF, or even plasma, was not included in any of the studies.

These facts not withstanding, within the constraints of the very limited, but deliberate focus of the submitted studies on assessing the potential neurotoxicity of the proposed drug product formulation relative to that of the RLD control product, this reviewer considers it a reasonable interpretation of the reported study data that there is no meaningful difference between the two in this regard. The reported analyses of plasma baclofen levels, across all three studies, appear to indicate that levels are comparable among all drug-treated groups after both 24 hours and 28 days of continuous infusion (though CSF levels were quite variable across studies and dose groups, with no explanation by the applicant). Clinical/neurological signs did not appear to differ significantly among the drug-treated groups, they appear to be pharmacologically driven, and they appear to diminish over the course of the infusion duration. And, in particular, the submitted data from all three definitive 28-day studies do appear to confirm that—under the specific conditions of these studies—there is no meaningful difference between the RLD and the proposed drug product formulation in their potential to induce granulomatous lesions along the spinal cord and/or in the intrathecal space. Indeed, the reported data do appear to support the applicant's assertion that it is the infusion apparatus itself, and not the infused baclofen formulation, that is responsible for inducing such a histopathological response.

Taken as a whole, this reviewer concludes the nonclinical data package deficient in providing positive assurance of safety for the specific proposed drug product formulation and drug infusion system combination product. However, the submitted nonclinical data do appear to support a conclusion that there is no meaningful difference in biological response within the intrathecal space of the dog chronically administered either the RLD or the proposed drug product formulation. Therefore, provided CMC review determines the proposed drug product quality and stability to be acceptable, this reviewer has no objections from a nonclinical perspective with a clinical review team decision in favor of approval.

6. Appendix/Attachments

30 April 2008 Pre-NDA Meeting
Sponsor Pharmacology / Toxicology Questions and Division Responses

(b) (4)

FDA preliminary response: Although we would generally ask for toxicity studies in two species, one might be sufficient considering the previous human experience with intrathecal baclofen. However, you will need to provide justification for testing in only one species and for your selection of species. We have the following comments on your proposed intrathecal study in dogs (based on the brief summary provided):

• Baclofen should be tested at a range of doses, including clinically relevant doses, up to a maximum tolerated dose (MTD). We would recommend that you conduct a dose-range finding study to determine an MTD. However, if you believe you have other data to support your dose selection, those data should be submitted for review.
• Consideration should be given to including an additional control group administered saline infused at the higher rate of 1 mL/day or to using 1 mL/day instead of 0.5 mL/day in the proposed vehicle control group.
• Conduct of clinical observations (including evaluation of proprioception) should be sufficiently rigorous to allow for assessment of the relationship between potential behavioral changes and local effects.
• For pivotal toxicity studies, we strongly recommend testing at least 4/sex/group.
• If local toxicity is observed, reversibility will need to be assessed.

If the data indicate cause for concern, additional nonclinical studies may need to be conducted.

(b) (4)

(b) (4)

Additional comments regarding the intrathecal toxicity study in dog:

• The Division stated that the purpose of the intrathecal study in dog is to assess toxicity, rather than pharmacodynamic activity, at the site of application; the primary local toxicity of concern is the development of granulomas.
• The Division confirmed the recommendation that 4/sex/group be used in the pivotal dog study.
• The Sponsor indicated the intent to conduct dose-range finding to support dose selection for the pivotal study.

CNS inquired whether there is any provision for pre-review of the published article and CNS' dose selection rationale, to determine whether it would be sufficient in this instance. The Agency responded that there is no provision for this type of pre-review.

(b) (4)

Also, please see response to Question 1.

Additional CMC Comment

With regard to the drug product specification, you propose a limit of NMT (b) (4) As this level exceeds the ICH qualification threshold, you will need to establish that this impurity has been adequately qualified by the intrathecal route. We acknowledge that the USP Baclofen Tablet monograph includes an acceptance criterion of NMT (b) (4). The USP limit, however, is only applicable to drug administered by the oral route. As there is no compendial monograph for Baclofen Injection, no public standard for acceptable levels of exposure to (b) (4) via the intrathecal route exists. Therefore, you would need to either demonstrate that comparable levels are present in the approved product, or qualify this impurity via appropriate nonclinical testing.

Q3. If additional preclinical studies are needed, please describe the nature of the study or studies required.

FDA preliminary response: please see responses to Questions 1 and 2.

Additional comment: please provide copies of published literature cited to support your IND/NDA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONALD C THOMPSON
03/03/2010

LOIS M FREED
03/03/2010
Please see memo for comments.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-462 **Applicant: CNS Therapeutics, Inc.** **Stamp Date: 30 Mar 2009**

Drug Name: Baclofen IT Inj. **NDA/BLA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		Both the hardcopy original submission and the requested additional electronic version appear to be appropriately organized.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		Both hardcopy and electronic versions appear to be appropriately indexed and paginated.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?		X	Nonclinical study reports 069-001 and 069-002 appear to be poor quality scanned copies, in which certain data tables are only poorly legible at best.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The sponsor's submission appears, on face, to contain all nonclinical data that were discussed and agreed to in the Type B pre-NDA meeting between the Division and the sponsor on 30 April 2008.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		IT route of administration
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			TBD
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes__X___No_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Submitted nonclinical study reports (Nos. 069-001 and 069-002) appear to be poor quality scanned copies, in which certain data tables are only poorly legible at best. The sponsor should be asked to generate and submit more clearly legible copies (hardcopy and electronic) of the noted study reports (Nos. 069-001 and 069-002).

D. Charles Thompson, R.Ph., Ph.D., D.A.B.T. — 13 July 2009
Reviewing Pharmacologist — Date

Lois Freed, Ph.D. — 13 July 2009
Team Leader/Supervisor — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donald C Thompson
7/13/2009 10:49:30 AM
PHARMACOLOGIST

Lois Freed
7/13/2009 06:33:11 PM
PHARMACOLOGIST