CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	215422
Priority or Standard	Standard
Submit Date(s)	January 22, 2021
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Division/Office	OND/DNP
Reviewer Name(s)	Susanne R. Goldstein, MD
Review Completion Date	10/22/2021
Established/Proper Name	Baclofen oral granules
(Proposed) Trade Name	Lyvisbah
Applicant	Saol Therapeutics Research Limited
Dosage Form(s)	Oral granules 5mg, 10mg and 20mg packet
Applicant Proposed Dosing Regimen(s)	Up to 20mg qid
Applicant Proposed Indication(s)/Population(s)	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of spasticity in adults and pediatric patients 12 years and older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Baclofen is a well-established muscle relaxant and antispastic drug. It is a GABA-B receptor agonist used for the treatment of spasticity), with a clinical profile well supported by more than 40 years of experience having been clinically introduced in Europe in 1966.

The precise mechanisms of action of baclofen are not fully known. It inhibits both monosynaptic and polysynaptic reflexes at the spinal level, probably by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects.

The currently approved oral tablet dosage forms of baclofen are indicated for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. It may also be of value in patients with spinal cord injuries and other spinal cord diseases. Baclofen treatment can aid in restoring residual function to those patients who have reversible spasticity.

Baclofen has been registered and commercially marketed globally for decades in an oral tablet dosage form of 10 and 20 mg for the treatment of spasticity, initially under the Lioresal® tradename, and in other generic forms. The determination of optimal dosage requires individual titration. Therapy initiates at a low dosage and increases gradually until an optimum effect is achieved (usually between 40 to 80 mg daily).

The following dosage titration schedule is suggested for the currently approved indication:
5 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days.

Thereafter additional increases may be necessary, but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.).

Baclofen Granule Development Rationale

Despite its longstanding commercial availability and usage, oral dosage forms of baclofen have until recently been limited to tablets. In September 2019, a solution oral form of baclofen was

also approved under the tradename Ozobax (Baclofen) Solution (5 mg/ 5mL), NDA 208193, by Metacel Pharmaceuticals LLC. Saol is seeking to provide an alternative oral form of therapy for patients that would provide for portability and ease of administration, for all required dose levels (5, 10, and 20 mg), especially for those patients with difficulty swallowing tablets. Baclofen granules are provided in a free-flowing granular form, packaged in a stick pack presentation. The development program was designed to demonstrate the bioequivalence to the currently approved oral tablet dosage form, while also providing data to demonstrate flexibility of the dosage forms administration, either to be administered with or without liquids, mixed into soft foods, or for tube feeding administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This is a 505(b)(2) application which utilized bioequivalence studies to bridge the efficacy and safety of the product to Lioresal (baclofen). The Office of Clinical Pharmacology has reviewed the results of the pivotal bioequivalence studies and concluded that baclofen granules are bioequivalent to Lioresal.

1.3. Benefit-Risk Assessment

The overall risk benefit assessment of baclofen granules is acceptable. Lioresal has been marketed in the United States for the treatment of spasticity since 1977 and has a well-characterized safety profile. No new adverse events were discovered in the course of the development program for baclofen granules that would affect the risk benefit assessment.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Spasticity is defined as a motor disorder, resulting from a single traumatic insult or chronic neurological diseases, and is characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of stretch reflexes arc. Spasticity of spinal origin (i.e., MS or SCI) is associated with the removal or destruction of supraspinal control and leads to increased excitability of motor neurons, while cerebral spasticity [i.e., traumatic brain injury (TBI), stroke, or cerebral palsy (CP)] results from a loss of descending inhibitory input from the brain. Spasticity can be functionally limiting and can lead to pain, diminished joint mobility, decreased muscle flexibility, and deformities if left untreated.

According to a North American Research Committee on Multiple Sclerosis (NARCOMS) patient registry survey, approximately 84% of MS patients experienced some degree of spasticity with 34% of patients rating their spasticity as moderate to severe (frequently affected or prevented daily activities). Treatment is indicated when spasticity interferes with activities of daily life and is accompanied by persistent spasms and muscle stiffness that can be painful and disabling.

2.2. Analysis of Current Treatment Options

Five drugs are approved in the US for the treatment of spasticity: baclofen (the RLD for this 505(b)(2) application), dantrolene, tizanidine, botulinum toxin products (Botox, Dysport, and Xeomin) and diazepam. These act in pharmacologically different mechanisms, though alteration of GABA neurotransmitter physiology is common to most. The toxins act at the peripheral neuromuscular junction.

Several other products related to those above or with a pharmacological action related to the pathophysiology of spasticity are used in off-label fashion. These include other benzodiazepines such as clonazepam, and anticonvulsants that also act via GABAergic mechanisms (e.g.: gabapentin).

Baclofen is an approved and currently marketed drug. The maximum single dose is 20 mg with the maximum daily dose of 20 mg qid (80 mg daily). The most common adverse event is transient drowsiness (10 to 63%). In one controlled study of 175 patients, transient drowsiness was observed in 63% of those receiving baclofen compared to 36% of those in the placebo group. Other common adverse reactions are dizziness (5 to 15%), weakness (5 to 15%) and fatigue (2 to 4%).

Recently, a liquid dosage form of baclofen, Ozobax, was approved in 2019.

3. Regulatory Background

3.1. Summary of Presubmission/Submission Regulatory Activity

Saol engaged with FDA on the development program proposals for Baclofen Granules, via a pre-IND meeting request (PIND 140719 Correspondence) dated December 20, 2018, for which written responses were provided on February 15, 2019 (reference PIND 140719). A summary of the meeting is provided below:

- that the proposed dosage form would be suitable for a 505(b)(2) NDA filing.
- a single dose pharmacokinetic (PK) study in healthy volunteers in an adult population, using the highest dose concentration (20mg) would be required.
- guided to conduct a food effect study with the new granule formulation, and to demonstrate the PK linearity/dose proportionality across the product strengths (5, 10, and 20 mg).

The IND was opened July 9, 2020; Study May Proceed letter was sent July 21, 2020.

The Initial Pediatric Study Plan was agreed upon on December 23, 2020:

- Proposed to advance the registration for Baclofen Granules with labeling for use in pediatrics (ages 12 and above) and adults, consistent with the current authorizations for Baclofen Tablets.
- Requested a waiver from any requirement to provide data from pediatric studies for the age group under 12 years of age.

PeRC agreed with the Pediatric Waiver Request, 10/25/2021.

4. Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

Table 1 Clinical Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose; Dosage Regimen (oral)	Number of Subjects Dosed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Bioavail -ability	Saol 1001-01 (Prot No. 190104)	Single dose fasted; test vs reference Baclofen Tablet	Open label, randomized 5-way crossover	A: Baclofen Tablets 20mg (Reference) with water B: Baclofen Granules 20mg, without water C: Baclofen Granules 20mg, with water D: Baclofen Granules 20mg, in soft food E: Baclofen Granules (4 x 5mg)	n=28	Healthy volunteers	Single dose exposure, 7 day washout between each treatment leg
PK	Saol 1001-02 (Prot No. 190342)	Single dose fasted vs fed; proportion-ality across dose range	Open label, randomized 4-way crossover	A: Baclofen Granules 20mg, with water, fasted B: Baclofen Granules 20mg, with water, fed C: Baclofen Granules 5mg, w water, fasted D: Baclofen Granules 10mg w/water, fasted	n=29	Healthy volunteers	Single dose exposure, 7 day washout between each treatment leg

Source: Sponsor

4.2. Review Strategy

The sponsor has submitted two clinical studies with the application, Study Saol 1001-01 (190104), bioavailability study, and Study Saol 1001-02 (190342), a pharmacokinetic study.

Baclofen is a currently approved and marketed medicinal substance in the US. The two bioequivalence protocols in this IND administer single doses of 20 mg of baclofen for comparison to the investigational product. This is well within the labeled approved dosing for this drug.

The studies will be reviewed for safety. No efficacy studies were submitted.

5. Review of Relevant Individual Trials Used to Support Safety

Study Saol 1001-01 (190104)

Title

A Single-Dose Fasted Comparative Bioavailability Study of Baclofen Granules and Baclofen Oral Tablets

Overview and Objective

Primary Objective:

To assess the systemic absorption and PK of a single 20 mg dose of baclofen granules when administered with water, without water or in soft foods, as compared to an established oral dose of baclofen tablets 20 mg in a fasted state.

Secondary Objective:

1. To assess the PK of four (4) sachets of 5 mg baclofen granules (20 mg dose total) to that of the single oral dose of baclofen tablets (20 mg), as a means of understanding the proportionality equivalence.
2. To assess the local tolerability (oral mucosa) of the oral granule formulation and to understand the safety profile relative to an oral tablet dose.

3. To assess the taste acceptability following the granule administration.

Trial Design

This was an open-label, randomized, five-way crossover, single-dose study comparing the PK of baclofen administered as an oral granule 20 mg presentation (whether with or without water or in soft foods) relative to that of a 20 mg oral baclofen tablet reference dose under fasting conditions. A total of 30 healthy, adult male and/or female smokers (no more than 25 cigarettes per day) and non-smoker subjects were planned to be included in this study and an estimated total of at least 26 healthy subjects were expected to complete the study. Prior to entering the trial, subjects had a screening visit to establish eligibility within 28 days before study drug administration. Subjects were randomized to receive a single dose (20 mg) of baclofen in a crossover approach in accordance with the randomization scheme generated by Syneos Health to receive each of Treatments A, B, C, D, and E in Periods 1 to 5 of the study as follows:

Treatment A: Baclofen tablets 20 mg;

Treatment B: Baclofen granules 20 mg, without water;

Treatment C: Baclofen granules 20 mg, with water;

Treatment D: Baclofen granules 20 mg, in soft food;

Treatment E: Baclofen granules 20 mg, with water, provided as 4 sachets of 5 mg each.

The single dose of assigned baclofen form was followed by a series of blood draws for PK analysis at pre-dose, 15, 30 and 45 minutes and at 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0, 24.0, and 48.0 hours post dosing.

A standard seven-day washout was used between single dose exposures of each assigned study period.

Safety was evaluated through assessment of adverse events, including oral mucosa evaluations, laboratory evaluations, vital signs and ECGs.

Table 2 Study Procedures and Evaluations

PROCEDURE	Screening[a] (D-28 to D-1)	Periods 1, 2, 3, 4, and 5				Study Exit[b]
		D-1	D1	D2	D3	

Informed Consent	X					
Eligibility	X		X			
Demographics	X					
Medical History	X					
Vital Signs	X	X	X[c]	X[c]	X[c]	X
ECG	X					
Physical Exam[d]	X					X
Hematology Labs[e]	X	X				X
Blood Chemistry Labs[e]	X	X				X
HIV and hepatitis	X					
Urinalysis	X					X
Urine Pregnancy Test	X					X
Serum Pregnancy Test		X				
Urine Drug Screen	X	X				
Alcohol Breath test	X	X				
Study Drug Administration[f]			X			
Blood Sample Collection for PK Testing[g]			X	X	X	
Concomitant Medications/ Procedures	X	X			X	X
Oral mucosa evaluation[h]	X		X	X		
Taste Acceptability Assessment[i]			X			
Adverse Events	X	X	X	X	X	X
Confinement		X	X			

a. All subjects fasted for 4 hours prior to the Screening Visit.

b. Corresponds to Day 3 of Period 5 or last visit in case of early termination.

c. Prior to dosing and at approximately 24 and 48 hours post treatment.

d. BMI was calculated at screening physical examination.

e. Laboratory assessments (i.e., hematology and blood chemistry) scheduled on Day -1 were done at check-in or in the morning of Day -1.

f. Study drug was administered in the morning following 10 hours of refraining from eating or drinking (with the exception of water). Additionally, water was prohibited for 1 hour prior to and 1 hour post study drug administration.

g. Blood samples for PK) analysis were collected at pre dose, 15, 30, and 45 minutes and at 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0, 24.0, and 48.0 hours post dosing.

h. Visual assessment of the tongue, palate, and buccal mucosa space were performed at screening, prior to baclofen granules dosing and at approximately 2 hours and 24 hours post dosing. Any alteration of the appearance would have been recorded as an AE.

i. Taste assessment was conducted and documented within 30 minutes of granule dosing (not required for tablet dose).

Source: Sponsor

Demographic Characteristics

A summary of demographic characteristics is presented in the table below for the per protocol population. The majority of subjects were of 'Not Hispanic or Latino (89.7%)' ethnicity and of 'White (96.6%)' race, with 3.4% of 'Black' race. Of the total population, 55.2% subjects were male and 44.8 as 43.7 years and the mean BMI was 24.631 kg/m^2.

Table 3 Summary of Demographic Characteristics of Subjects Included in the Per Protocol Population

Category	Statistic	Treatment A (N=29)	Treatment B (N=29)	Treatment C (N=28)	Treatment D (N=29)	Treatment E (N=29)	Overall (N=29)
Age (years)	N	29	29	28	29	29	29
	Mean	43.7	43.7	43.4	43.7	43.7	43.7
	SD	9.0	9.0	9.0	9.0	9.0	9.0
	Median	44.0	44.0	44.0	44.0	44.0	44.0
	Min, Max	20, 55	20, 55	20, 55	20, 55	20, 55	20, 55
Age Groups							
<18	n (%)	0	0	0	0	0	0
18-40	n (%)	11 (37.9)	11 (37.9)	11 (39.3)	11 (37.9)	11 (37.9)	11 (37.9)
>40	n (%)	18 (62.1)	18 (62.1)	17 (60.7)	18 (62.1)	18 (62.1)	18 (62.1)
Gender							
Female	n (%)	13 (44.8)	13 (44.8)	13 (46.4)	13 (44.8)	13 (44.8)	13 (44.8)
Male	n (%)	16 (55.2)	16 (55.2)	15 (53.6)	16 (55.2)	16 (55.2)	16 (55.2)
Ethnicity							
Not Hispanic or Latino	n (%)	26 (89.7)	26 (89.7)	25 (89.3)	26 (89.7)	26 (89.7)	26 (89.7)
Hispanic or Latino	n (%)	3 (10.3)	3 (10.3)	3 (10.7)	3 (10.3)	3 (10.3)	3 (10.3)

Category	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Overall

	Statistic	(N=29)	(N=29)	(N=28)	(N=29)	(N=29)	(N=29)
Race							
White	n (%)	28 (96.6)	28 (96.6)	27 (96.4)	28 (96.6)	28 (96.6)	28 (96.6)
Black	n (%)	1 (3.4)	1 (3.4)	1 (3.6)	1 (3.4)	1 (3.4)	1 (3.4)
Asian	n (%)	0	0	0	0	0	0
Am Indian	n (%)	0	0	0	0	0	0
Hawaiian	n (%)	0	0	0	0	0	0
Multi-racial	n (%)	0	0	0	0	0	0
Other	n (%)	0	0	0	0	0	0
Height (cm)	N	29	29	28	29	29	29
	Mean	167.90	167.90	167.66	167.90	167.90	167.90
	SD	8.70	8.70	8.76	8.70	8.70	8.70
	Median	168.00	168.00	167.25	168.00	168.00	168.00
	Min, Max	152.0, 188.0	152.0, 188.0	152.0, 188.0	152.0, 188.0	152.0, 188.0	152.0, 188.0
Weight (kg)	N	29	29	28	29	29	29
	Mean	69.92	69.92	69.75	69.92	69.92	69.92
	SD	12.46	12.46	12.65	12.46	12.46	12.46
	Median	68.20	68.20	66.60	68.20	68.20	68.20
	Min, Max	46.0, 97.6	46.0, 97.6	46.0, 97.6	46.0, 97.6	46.0, 97.6	46.0, 97.6

Category	Statistic	Treatment A (N=29)	Treatment B (N=29)	Treatment C (N=28)	Treatment D (N=29)	Treatment E (N=29)	Overall (N=29)
BMI (kg/m^2)	N	29	29	28	29	29	29
	Mean	24.631	24.631	24.636	24.631	24.631	24.631
	SD	2.752	2.752	2.802	2.752	2.752	2.752
	Median	24.900	24.900	24.910	24.900	24.900	24.900
	Min, Max	19.91, 29.28	19.91, 29.28	19.91, 29.28	19.91, 29.28	19.91, 29.28	19.91, 29.28

N: Number of subjects dosed; n (%): Number and percent of subjects; SD: Standard Deviation.
Am Indian: American Indian or Alaskan Native; Black: Black or African American; Hawaiian: Native Hawaiian or Pacific Islander; BMI: body mass index. Last results (scheduled or unscheduled) obtained at screening were used to generate this table.
Treatment A: Baclofen tablets 20mg; Treatment B: Baclofen granules 20mg, without water; Treatment C: Baclofen granules 20mg, with water; Treatment D: Baclofen granules 20mg, in soft food; Treatment E: Baclofen granules 20mg, with water, provided as 4 stick packs of 5mg each.
Data source: Listing 16.2.4-1
Source: Sponsor

Study Saol 1001-02 (190342)

A Single-Dose Comparative Bioavailability Study of Baclofen Granules

Overview and Objective

Primary:

To assess the systemic absorption and PK of a single 20 mg dose of baclofen granules when administered with water in the fasted state (1) as compared with the same dose administration taken in the fed state and (2) to assess the dose-proportionality of the PK across the dose range of 5 mg, 10 mg, and 20 mg with water in a fasted state.

Secondary:
1. To assess the local tolerability (oral mucosa) of the oral granule formulation and to understand the safety profile.
2. To assess the taste acceptability following the granule administration.

Trial Design

Study Saol 1001-02 (190342) was a randomized four-way single-dose crossover study to compare the PK of baclofen administered as a 20 mg oral dose of granule formulation under fed versus fasted conditions, in addition to assessing the dose-proportionality of the PK across the dose range of 5 mg, 10 mg, and 20 mg granules.

Healthy Volunteers were administered one of the following treatments:

- Treatment A: Baclofen granules 20 mg, with water, fasted;
- Treatment B: Baclofen granules 20 mg, with water, fed;
- Treatment C: Baclofen granules 5 mg, with water, fasted;
- Treatment D: Baclofen granules 10 mg, with water, fasted.

The single dose of assigned baclofen form was followed by a series of blood draws for PK analysis at pre-dose, 15, 30 and 45 minutes and at 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0, 24.0, and 48.0 hours post dosing. A standard seven day washout was used between single dose exposures of each assigned study period.

Safety was evaluated through assessment of adverse events, including oral mucosa evaluations, laboratory evaluations, vital signs and ECGs.

Table 4 Study Procedures and Evaluations

PROCEDURE	Screening[a] (D-28 to D-1)	Periods 1, 2, 3, and 4				Study Exit[b]
		D-1	D1	D2	D3	
Informed Consent	X					
Eligibility	X		X			
Demographics[j]	X					
Medical History	X					
Vital Signs	X	X	X[c]	X[c]	X[c]	X
ECG	X					
Physical Exam[d]	X					X
Hematology Labs[e]	X	X				X
Blood Chemistry Labs[e]	X	X				X
HIV and hepatitis	X					
Urinalysis	X					X
Urine Pregnancy Test	X					X
Serum Pregnancy Test		X				
Urine Drug Screen	X	X				
Alcohol Breath test	X	X				
Study Drug Administration[f]			X			
Blood Sample Collection for PK Testing[g]			X	X	X	
Concomitant Medications/ Procedures	X	X			X	X
Oral Mucosa Evaluation[h]	X		X	X		
Taste Acceptability Assessment[i]			X			
Adverse Events	X	X	X	X	X	X
Confinement		X	X			

a. All subjects fasted for 4 hours prior to the Screening Visit.
b. Corresponds to Day 3 of Period 4 or last visit in case of early termination.
c. Prior to dosing and at approximately 24 and 48 hours post treatment.
d. BMI was calculated at screening physical examination.
e. Laboratory assessments (i.e., hematology and blood chemistry) scheduled on Day -1 were done at check-in or in the morning of Day -1.
f. Subjects assigned to Treatments A, C, and D, were refrained from eating or drinking (with the exception of water) for at least 10 hours prior to each administration of study drug, until approximately 4.5 hours after dosing. Except for water given with study medication, no fluids were allowed from 1 hour before dosing until 1 hour post-dose.
For subjects assigned to Treatment B, after a supervised fast of at least 10 hours, subjects were served a critical, high-fat, meal. Subjects were required to start their meal as soon as it is served and to complete it in 30 minutes or less. Drug administration was occured 30 ± 1 minutes after the meal has been kstarted. Subjects will fast for not less than 4.5 hours after drug administration.
g. Blood samples for PK analysis were collected at pre dose (0.000), 0.250, 0.500, and 0.750 minutes and at 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0, 24.0, and 48.0 hours post dosing.

h. Visual assessment of the tongue, palate, and buccal mucosa space will be performed at screening, prior to baclofen granules dosing and at approximately 2 hours and 24 hours post dosing. Any alteration of the appearance will be recorded as an adverse event (AE).
There were no new safety findings that would modify the currently approved product labeling, and a specific assessment of the oral mucosa local tolerability both pre and post dosing revealed no adverse effects. Study volunteers further affirmed the acceptability of the formulations taste.
i. Taste assessment to be conducted and documented within 30 minutes of granule dosing administration.
j. Demographic information collected at Screening will include gender, date of birth, race, ethnicity, height, and weight.

Source: Sponsor

Demographic Characteristics

Most of the subjects were male (71.4%) and White (96.4%), non-Hispanic or Latino (71.4%), with mean age of 41.8 years old and mean BMI of 25.705 kg/m^2 for the safety population. There was no imbalance among the treatment groups since the study was crossover in nature.

Table 5 Summary of Demographic Characteristics of Subjects Included in the Per Protocol Population

Category	Statistic	Treatment A (N=28)	Treatment B (N=26)	Treatment C (N=27)	Treatment D (N=27)	Overall (N=28)
Age (years)	N	28	26	27	27	28
	Mean	41.8	42.0	41.5	41.5	41.8
	SD	9.2	9.1	9.2	9.2	9.2
	Median	44.5	44.5	44.0	44.0	44.5
	Min, Max	28, 54	28, 54	28, 54	28, 54	28, 54
Age Groups						
<18	n (%)	0	0	0	0	0
18-40	n (%)	12 (42.9)	11 (42.3)	12 (44.4)	12 (44.4)	12 (42.9)
>40	n (%)	16 (57.1)	15 (57.7)	15 (55.6)	15 (55.6)	16 (57.1)
Gender						
Female	n (%)	8 (28.6)	7 (26.9)	7 (25.9)	7 (25.9)	8 (28.6)
Male	n (%)	20 (71.4)	19 (73.1)	20 (74.1)	20 (74.1)	20 (71.4)
Ethnicity						
Not Hispanic or Latino	n (%)	20 (71.4)	19 (73.1)	20 (74.1)	20 (74.1)	20 (71.4)
Hispanic or Latino	n (%)	8 (28.6)	7 (26.9)	7 (25.9)	7 (25.9)	8 (28.6)

Category	Statistic	Treatment A (N=28)	Treatment B (N=26)	Treatment C (N=27)	Treatment D (N=27)	Overall (N=28)
Race						
White	n (%)	27 (96.4)	25 (96.2)	26 (96.3)	26 (96.3)	27 (96.4)
Black	n (%)	1 (3.6)	1 (3.8)	1 (3.7)	1 (3.7)	1 (3.6)
Asian	n (%)	0	0	0	0	0
Am Indian	n (%)	0	0	0	0	0
Hawaiian	n (%)	0	0	0	0	0
Multi-racial	n (%)	0	0	0	0	0
Other	n (%)	0	0	0	0	0
Height (cm)	N	28	26	27	27	28
	Mean	170.16	170.55	170.44	170.44	170.16
	SD	8.31	8.49	8.33	8.33	8.31
	Median	170.75	171.75	171.50	171.50	170.75
	Min, Max	156.5, 187.5	156.5, 187.5	156.5, 187.5	156.5, 187.5	156.5, 187.5
Weight (kg)	N	28	26	27	27	28
	Mean	74.52	75.09	74.52	74.52	74.52
	SD	8.98	8.46	9.15	9.15	8.98
	Median	76.60	76.60	77.00	77.00	76.60
	Min, Max	55.4, 92.2	57.0, 92.2	55.4, 92.2	55.4, 92.2	55.4, 92.2

N: Number of subjects dosed; n (%): Number and percent of subjects; SD: Standard Deviation.
Am Indian: American Indian or Alaskan Native; Black: Black or African American; Hawaiian: Native Hawaiian or Pacific Islander; BMI: body mass index. Last results (scheduled or unscheduled) obtained at screening were used to generate this table.
Treatment A: Baclofen granules 20mg, with water, fasted; Treatment B: Baclofen granules 20mg, with water, fed; Treatment C: Baclofen granules 5mg, with water, fasted; Treatment D: Baclofen granules 10mg, with water, fasted.
Data source: Listing 16.2.4-1

Source: Sponsor

6. Review of Safety

6.1. Safety Review Approach

To summarize the disposition and exposure data, summary table displays were prepared which combine the common treatments across both studies into a 2-column display. Column 1 combines Treatment A from study 02 and Treatment C from study Saol 1001-01 (both arms have in common the 20 mg granule dose with water). As there were no new treatment-related safety issues, column 2 combines all the 20 mg granule arms across both studies as follows:

Treatments A and B from study Saol 1001-01(Protocol 190104), and Treatments B, C, D, and E from study Saol 1001-02 (Protocol 190342).

6.1.1. Overall Exposure

Table 6 Exposure

	Baclofen granules 20mg with water N- 59 n (&)	Baclofen granules 20mg N-59 n (&)
Number of subjects who completed all study periods	54 (91.5)	54 (91.5)
Number of subjects who did not complete the study	5 (8 5)	5 (8 5)

Source: Sponsor

6.2. Safety Results

6.2.1. Deaths

None

6.2.2. Serious Adverse Events

Study SAOL 1001-02, one subject experienced an SAE of "Thrombotic stroke"

Subject Number	Treatment	Serious Adverse Event	Relationship
(b) (6)	Treatment A	Thrombotic stroke	Unrelated

Treatment A: Baclofen granules 20 mg, with water, fasted; Treatment B: Baclofen granules 20 mg, with water, fed; Treatment C: Baclofen granules 5 mg, with water, fasted; Treatment D: Baclofen granules 10 mg, with water, fasted Data source: Listing 16.2.7-3
Source: Sponsor

Four days after the first dose (Treatment A) of Period 1 ((b) (6)), the 55-year-old male subject was found to have a thrombotic stroke. The symptoms experienced included dizziness, fatigue, trouble with vision, difficulty speaking clearly, slowness in speaking and difficulty in differentiating between reality and a dream. The intensity of all symptoms started to decrease by the end of the afternoon on (b) (6) but were still severe. The subject did not take any medication, drugs, or alcohol since the last dosing date. In the morning of (b) (6), the severity of all symptoms decreased to moderate. On (b) (6), the severity decreased to mild as per subject. The troubled vision, difficulty speaking clearly, slowness in speaking and difficulty in differentiating between reality and a dream had resolved at the end of the afternoon on (b) (6).

Considering the severity of all the symptoms, the nurse strongly suggested and urged the subject to get a consultation at the hospital as soon as possible. The subject was also warned not to drive his car. There was no headache, nausea, vomiting, paresthesia, or sagging of the face according to the subject. On (b) (6), a nurse from the emergency department called the study nurse in order to obtain information regarding the subject. The emergency department had taken charge of the subject.

The PI had a phone discussion with the neurologist on (b) (6). The subject was hospitalized for a thrombotic stroke. The subject had a CT scan showing an ischemic lesion and was awaiting an MRI. The PI had a phone discussion on (b) (6) with the neurologist. The subject was still hospitalized and in stable condition. Based on the brain MRI, he had an ischemic lesion on the left thalamic area that correlates well with subject's symptoms: slight confusion, memory loss and language difficulty. Once the hospital stay was completed, he needed to go through a rehabilitation process.

REVIEWER COMMENT: Based on timing of study drug administration and occurrence of this event, it is unlikely to be drug related.

6.2.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

The safety population that shared a common exposure to the 20 mg baclofen across both studies was pooled, providing for a disposition summary which is provided in the table below. Fifty-four of the fifty-nine subjects from the safety population completed all treatment periods. Of the 5 subjects who discontinued, two were due to adverse events.

Table 7 Patient Disposition

Category	Baclofen granules 20mg with water N=59 n (%)	Baclofen granules 20mg N=59 n (%)
Completed All Treatment Periods[1]	54 (91.5)	54 (91.5)
Number of Subjects Discontinued[2]	5	5
Primary Reason for Discontinuation[2,3]		
Adverse Event	2 (40.0)	2 (40.0)
Pregnancy	0	0
Death	0	0
Protocol Deviation	0	0
Lost to Follow-up	0	0
Study Termination by Sponsor	0	0
Non-Compliance with Study Drug	0	0
Withdrawal by Subject	0	0
Physician Decision	1 (20.0)	1 (20.0)
Other	2 (40.0)	2 (40.0)

Source: Sponsor

Five subjects discontinued from the study prematurely: 2 for adverse events, 1 for physician decision, and 2 for “other”. Both of the withdrawal events occurred during study Saol 1001-02; one SAE “Thrombotic stroke” and one significant AE “Pruritus”. The case of pruritus was judged possibly related to the baclofen therapy and the event resolved without medication after 20 days. The case of thrombotic stroke occurred in a subject four days post his first dose of the baclofen study medication. The subject was hospitalized, later stabilized and dismissed from the hospital. The subject was withdrawn from the clinical study as a result of the event.

6.2.4. **Treatment Emergent Adverse Events and Adverse Reactions**

Saol 1001-01

A total of 85 TEAEs were reported by 24 of the 30 subjects who received any amount of the study drug (ITT population). The most commonly reported TEAEs during this study were related to the system organ class: nervous system. TEAEs reported in more than 1 subject consisted of Somnolence (27 TEAEs in 14 subjects overall) followed by Dizziness (10 TEAEs in 7 subjects overall), Headache (6 TEAEs in 6 subjects overall), and Disturbance in attention (3 TEAEs in 3 subjects overall). All other TEAEs were each reported by no more than 1 subject by treatment group. Most events were mild in severity. There were no serious or significant AEs reported

during this study.

Saol 1001-02

A total of 31 TEAEs were reported by 12 (41.4%) of the 29 subjects who received any amount of the study medication (safety population). Of these, 11 TEAEs were reported by six subjects who received Treatment A, seven TEAEs were reported by five subjects who received Treatment B, seven TEAEs were reported by five subjects who received Treatment C, and six TEAEs were reported by four subjects who received Treatment D.

REVIEWER COMMENT: No new safety signals were identified.

6.2.5. Laboratory Findings

There were no TEAEs related to laboratory abnormalities in study Saol 1001-01.

In study Saol 1001-02 there was a clinically significant laboratory finding that was considered a TEAE. A subject had been performing strenuous exercises at the gym prior to returning to the clinic for the assigned visit. This resulted in abnormal aspartate aminotransferase and blood creatine phosphokinase increases on laboratory assessment.

Subj. No.	Trtmt	Adverse Event (Preferred Term)	Test Normal Range	Baseline Result	Clinically Significant Result	Repeat	Resolution
(b) (6)	Treatment D	Aspartate Aminotransferase Increased	10-35 (U/L)	245 (U/L)	245 (U/L)	52 (U/L)	Recovered/Resolved
(b) (6)	Treatment D	Blood Creatine Phosphokinase Increased	40-195 (U/L)	8503 (U/L)	8503 (U/L)	170 (U/L)	Recovered/Resolved

Treatment A: Baclofen granules 20 mg, with water, fasted; Treatment B: Baclofen granules 20 mg, with water, fed; Treatment C: Baclofen granules 5 mg, with water, fasted; Treatment D: Baclofen granules 10 mg, with water, fasted Data source: Listing 16.2.7-2

The subject was advised to discontinue the strenuous activity and the levels returned to baseline. The incident was not related to baclofen therapy.

6.2.6. Vital Signs

Abnormalities in vital sign results were observed for a number of parameters at one or more assessments; however, none of these abnormalities were considered clinically significant. No TEAEs related to vital signs abnormalities were recorded. The abnormal values generally occurred in subjects with low or high baseline values that were not notably different from the

post-dose results.

6.2.7. Electrocardiograms (ECGs)

No clinically significant on-study ECG assessments were reported during this study.

7. Labeling Recommendations

7.1. Prescription Drug Labeling

This is a 505(b)(2) application. The applicant is relying on the findings of safety and efficacy of Lioresal (baclofen). (NDA). The label will be consistent with the prescribing information for FDA-approved label for Lioresal. In addition, the Ozobax label will be used as template for the updated PLLR format for baclofen oral granules label.

7.2. Nonprescription Drug Labeling

N/A

8. Postmarketing Requirements and Commitments

N/A

9. Appendices

9.1. References

N/A

9.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 11		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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11/04/2021 02:55:03 PM

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11/04/2021 03:19:04 PM