CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	215602
Priority or Standard	Standard
Submit Date(s)	April 5, 2021
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PDUFA Goal Date	February 5, 2022
Division/Office	OND/DNP
Reviewer Name(s)	Susanne R. Goldstein, MD
Review Completion Date	January 31, 2022
Established/Proper Name	Baclofen oral suspension
(Proposed) Trade Name	Fleqsuvy
Applicant	Azurity Pharmaceuticals
Dosage Form(s)	Oral solution 5mg/mL
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.

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.).

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 approved under the tradename Ozobax (Baclofen) Solution (5 mg/ 5mL), NDA 208193, by Metacel Pharmaceuticals LLC. In October 2021, oral granule form of baclofen was also approved under the tradename Lyvispah, NDA 215422, by Saol Therapeutics Research Limited.

Baclofen Oral Suspension Development Rationale

Azurity Pharmaceuticals has developed a dosage form that can be administered to patients who have difficulty swallowing tablets and additionally offering flexibility in dose titration for

baclofen which is known to have a narrow therapeutic index.

The proposed indication for Baclofen Oral Suspension (5 mg/mL) is for the treatment of spasticity resulting from MS, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity in adults and adolescents 12 years of age and older. Baclofen Oral Suspension may also be of some value in patients with spinal cord injuries and other spinal cord diseases. The applicant is seeking approval of NDA 215602 under the provisions of 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

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 oral suspension is bioequivalent to Lioresal.

1.3. Benefit-Risk Assessment

The overall risk benefit assessment of baclofen oral suspension 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 oral suspension 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, and oral granules, Lyvispah, was approved in 2021.

3. Regulatory Background

3.1. Summary of Presubmission/Submission Regulatory Activity

Azurity engaged with FDA on the development program proposal for Baclofen oral suspension, via a pre-IND meeting request (PIND 133462) Written Responses, February 17, 2017.

Clinical Review
{Susanne R. Goldstein}
{NDA 215602
{Fleqsuvy, baclofen oral suspension}

In response to a meeting request, the following advice was offered after review of a background brief submitted by the sponsor on January 19, 2017 (clinically relevant items only):

Question 2: *Does the Agency agree that Baclofen Tablets USP* (b) (4) *is the appropriate reference listed drug (RLD)?*

FDA Response to Question 2:
No. (b) (4)

Please note, however, that if you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug that is discontinued from marketing and you intend to support the scientific appropriateness of such reliance through a comparative bioavailability study, it is recommended that you use the ANDA product designated as the reference standard in the Orange Book to establish a bridge between your proposed drug product and the specified listed drug.

The applicant proposed a single dose, crossover study of their baclofen oral solution 5 mg/mL (4 mL for 20 mg) to the (b) (4) 20 mg baclofen tablet in fasted state. No other human studies were proposed.

Question 9: *Does the Agency agree that the design of the proposed clinical study is adequate to support a 505(b)(2) NDA?*
FDA Response to Question 9:
The proposed study seems adequate to bridge the baclofen oral suspension to the RLD product. In addition, you will need to evaluate the food effect for the new formulation.

The IND was opened December 21, 2016; Study May Proceed letter was sent January 17, 2018.

The Initial Pediatric Study Plan was agreed upon on June 6, 2018.

- Proposed to advance the registration for Baclofen Oral Suspension 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 Pediatric Waiver Request, December 14, 2021.

4. Sources of Clinical Data and Review Strategy

4.1. Review Strategy

The sponsor has submitted a Phase 1 bioavailability study with the application, Study RM-05-PK001.

Baclofen is a currently approved and marketed medicinal substance in the US. The bioequivalence protocol 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 study will be reviewed for safety. No efficacy studies were submitted.

5. Review of Relevant Individual Trials Used to Support Efficacy

Study RM-05-PK001

A Randomized, Open-Label, Single-Dose, 3-Way Relative Bioavailability Study of 20 mg of Baclofen Oral Suspension 5mg/mL (4 mL) under Fed and Fasted Conditions and Baclofen Tablet USP, 20 mg under fasted Conditions in Healthy Adult Volunteers

5.1.1. Study Design

Overview and Objective

Primary Objective:
• To determine the relative bioavailability of 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL) and Baclofen Tablet, USP (20 mg) under fasted conditions in healthy adult male and female volunteers

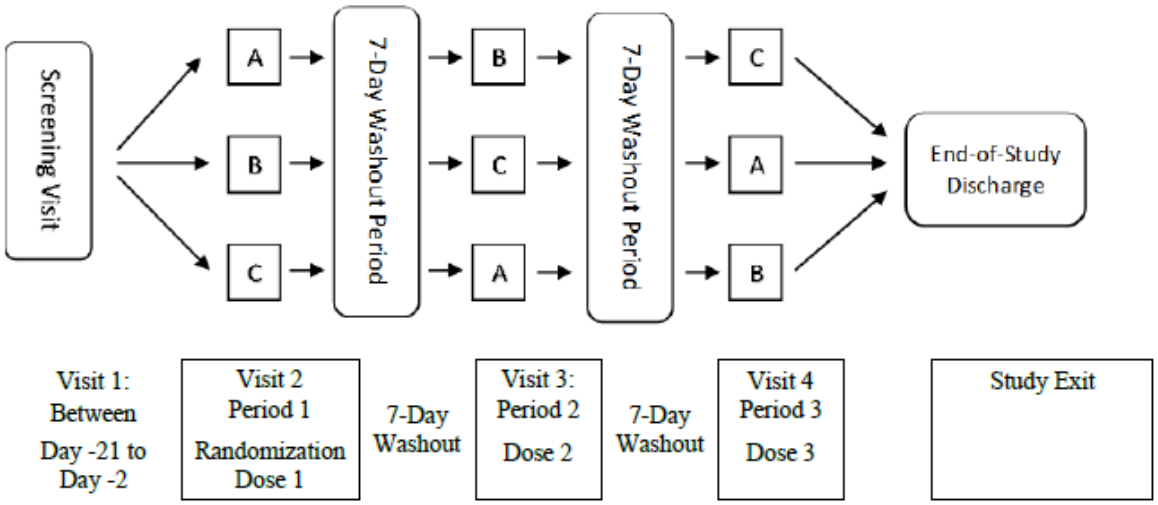
• To assess the effect of food on the absorption of 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL) by administering the formulation under fed versus fasted conditions in healthy adult male and female volunteers.

Secondary Objective:
• To evaluate the safety and tolerability of single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL (4 mL) versus Baclofen Tablet, USP (20 mg) in healthy adult male and female volunteers.

Trial Design

This was an open-label, randomized, three-period, crossover design study to evaluate the relative bioavailability of a single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL (4 mL) under fasted versus a single oral dose of Baclofen Tablets, USP (20 mg) under fasted conditions and a single 20 mg oral dose of Baclofen Oral Suspension 5 mg/mL under fed conditions in healthy male and female subjects.

Figure 1 Trial Design



Treatment A	Test (Fasted): Single 20 mg oral dose suspension of Baclofen Oral Suspension 5 mg/mL (4 mL) under fasted conditions.
Treatment B	Test (Fed): Single 20 mg oral dose suspension of Baclofen Oral Suspension 5 mg/mL (4 mL) under fed conditions (following a high-fat, high-calorie meal).
Treatment C	Reference (Fasted): Single oral dose of Baclofen Tablets, USP (20 mg) under fasted conditions.

Source: Sponsor

Eligible subjects received a single oral dose of study drug as three study treatments (Treatment A, B or C) on three separate periods in a randomly assigned sequence, with each treatment separated by an approximate 7-day washout period. In each study period (Day 1 of Periods 1, 2 and 3), dosing occurred in the morning after an overnight fast of at least 10 hours. Study drug was administered with 240 mL of room temperature water.

PK Sampling: In each of the three study periods, serial PK blood samples to measure plasma concentrations of baclofen were collected at pre-dose (up to 60 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0-, and 24-hours post-dose in each period.

High-fat meal Breakfast for Fed Treatment
After an overnight fast of approximately 10 hours, the following high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) breakfast was consumed by subjects receiving the test formulation under fed conditions. Subjects began consuming a high-fat meal breakfast approximately 30 minutes prior to dosing and completely consumed the meal approximately 5 minutes prior to dosing. This breakfast contained

approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories.

Table 1 Study Procedures and Evaluations

Activity	Screening (Days -21 to -2)	Study Period	Study Days[a]			Study Exit or Early Withdrawal[b]
			Check-in	Confinement		
		1	-1	1	2	
		2	-1	1	2	
		3	-1	1	2	
Informed consent	X					
Inclusion/Exclusion criteria	X		X			
Medical/surgical history	X		X			
Demographic information	X					
Physical examination[i]	X		X			X
Blood pressure, pulse rate	X		X[d]	X[d]	X[d]	X
Respiratory rate	X					
Oral temperature	X					
Height and weight	X					
Resting 12-lead ECG[c]	X					
Clinical laboratory (hematology, chemistry, urinalysis) tests[j]	X				X	X
Hepatitis/HIV serology	X					
Urine pregnancy[e]	X		X			X
Drug/alcohol screen	X		X			
Admission to Clinic			X			
Randomization (Day 1 only)				X		
Standardized meals[k]			X	X	X	
Overnight fast			X[f]			
High fat breakfast				X[g]		
Administer study drug				X[g]		
PK sampling				X[h]	X[h]	
Discharge from Clinic					X	
Prior/Concomitant medications			X	X	X	X
Adverse events			X	X	X	X

a. On each of the 3 study periods, volunteers will be confined to the clinical study unit from approximately 1400-1600 hours on the day prior to dosing until 24h post-dose. Volunteers will then be permitted to leave the study unit after the 24 hour PK sample collection for period 1, 2 and 3.
b. Exit procedures are to be performed after collection of the 24h PK sample and clinical assessments in Period 3 or if a subject has early withdrawal and is discharged from the study prior to the 24h assessments on Period 3.
c. ECG will be taken after a 5 minute rest period.
d. Vital signs (resting sitting systolic blood pressure, diastolic blood pressure and pulse rate) will be obtained within 120 minutes pre-dose and at 1, 4, 6, 8, 10, 12 and 24h post-dose and at study exit.
e. Urine pregnancy test will be performed at Screening, at each Check-in Visit and at Study Exit/Early Termination for all female volunteers.
f. All volunteers will fast overnight for at least 10 hours prior to study drug administration.
g. For Fed treatment only: following an overnight fast of at least 10 hours, volunteers will begin consuming a high fat high calorie breakfast approximately 30 minutes prior to dosing and will completely consume the meal approximately 5 minutes prior to dosing. Volunteers will then receive a single oral dose of the test formulation with approximately 240 mL of room temperature water at approximately 0800 hours (± 1 hour).
h. PK samples to be collected prior to (pre-dose, within 60 minutes prior to dosing) study drug administration and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours post-dose.
i. A full PE will be performed at Screening, and an abbreviated PE will be performed at the Check-in Visit on Day -1 and at the Study Exit/Early Termination Visit.
j. Clinical chemistry tests will be conducted at the Screening Visit, at 24-hour post-dose in each Period and at Study Exit/Early Termination. If clinical chemistry at 24-hour post-dose coincide with at Study Exit/Early Termination, duplicated testing will not be performed. Hematology and urinalysis will be conducted at Screening Visit and at Study Exit/Early Termination.
k. Standardized meals will be given prior to 2100 hours on the day prior to dosing. Lunch will be provided 4 hours post-dose on dosing days. Dinner and evening snacks will be given at standard meal time.

Source: Sponsor

Study Endpoints

Pharmacokinetic:

Plasma concentrations of Baclofen will be measured. Pharmacokinetic parameters for Baclofen including Cmax, tmax, AUC0-t, AUC0-∞, Kel and t1/2 will be calculated using a non-compartmental analysis method.

Safety: The occurrence of all AEs reported through the completion of study will be collected and evaluated. Clinical laboratory parameters (hematology, chemistry, urinalysis), vital signs (seated systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature), ECGs and physical examination data will be collected and evaluated relative to baseline values.

Statistical Analysis Plan

Parameters and Statistical criteria for PK comparison
Pharmacokinetic parameters for baclofen including C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} and $t_{1/2}$ were calculated using a non-compartmental analysis method. The relative bioavailability between

the Test formulation – 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL) fasted vs. Reference formulation – Baclofen Tablets USP (20 mg), fasted and food effect between 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL), fasted vs. - 20 mg of Baclofen Oral Suspension 5 mg/mL (4 mL), fed were considered not significant if the 90% CI for the ratios of geometric means from the ANOVA model of the Log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} are within 80.00% to 125.00%.

Demographic Characteristics

Subjects were healthy adult males (n=23, 82.5%) and females (n=4, 14.8%) ranging from 24-54 years of age. Overall mean (SD) age was 39.5 (9.87) years. Twenty-three (82.5%) of subjects were Black/African-American, and 4 (14.8%) of the subjects were White. There was no imbalance among the treatment groups since the study was crossover in nature**.**

Table 2 of Demographic Characteristics

Parameter	Baclofen Oral Suspension 5mg/mL (4mL) Fasted (N=25) n(%)	Baclofen Oral Suspension 5mg/mL (4mL) Fed (N=25) n(%)	Baclofen Tablet USP 20 mg Fasted (N=25) n(%)	All Subjects (N=27) n(%)
Age (years)				
n	25	25	25	27
Mean (SD)	40.2 (9.95)	39.8 (9.74)	39.6 (10.03)	39.5 (9.87)
Median	39.0	38.0	38.0	38.0
Min, Max	24, 54	24, 54	24, 54	24, 54
Age Group (years), n(%)				
18 - 40	14 (56.0)	15 (60.0)	15 (60.0)	16 (59.3)

Parameter	Baclofen Oral Suspension 5mg/mL (4mL) Fasted (N=25) n(%)	Baclofen Oral Suspension 5mg/mL (4mL) Fed (N=25) n(%)	Baclofen Tablet USP 20 mg Fasted (N=25) n(%)	All Subjects (N=27) n(%)
41 - 55	11 (44.0)	10 (40.0)	10 (40.0)	11 (40.7)
Gender, n (%)				
Male	21 (84.0)	21 (84.0)	21 (84.0)	23 (85.2)
Female	4 (16.0)	4 (16.0)	4 (16.0)	4 (14.8)
Race, n (%)				
Black or African American	21 (84.0)	21 (84.0)	21 (84.0)	23 (85.2)
White	4 (16.0)	4 (16.0)	4 (16.0)	4 (14.8)
Ethnicity, n (%)				
Hispanic or Latino	5 (20.0)	5 (20.0)	5 (20.0)	5 (18.5)
Non-Hispanic or Non-Latino	20 (80.0)	20 (80.0)	20 (80.0)	22 (81.5)
Weight (kg)				
n	25	25	25	27
Mean (SD)	78.98 (10.199)	79.80 (10.106)	79.82 (10.135)	79.90 (10.359)
Median	77.70	79.10	79.10	79.10
Min, Max	62.3, 103.2	62.3, 103.2	62.3, 103.2	62.3, 103.2
Height (cm)				
n	25	25	25	27
Mean (SD)	172.94 (9.205)	173.64 (9.162)	173.36 (8.969)	173.33 (9.053)
Median	175.00	175.00	175.00	175.00
Min, Max	156.0, 192.0	156.0, 192.0	156.0, 192.0	156.0, 192.0
BMI (kg/m^2)				
n	25	25	25	27
Mean (SD)	26.38 (2.404)	26.44 (2.369)	26.54 (2.483)	26.56 (2.406)
Median	26.40	26.40	26.40	26.40
Min, Max	21.1, 30.8	21.1, 30.8	21.1, 30.8	21.1, 30.8

n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population under each treatment
Source: Table 14.1.4

Source: Sponsor

6. Review of Safety

6.1. Review of the Safety Database

6.1.1. Overall Exposure

A total of 27 healthy adult male and female subjects were randomized equally to three crossover treatment sequences.

A total of 25 subjects (92.6%) completed the study. Twenty-three subjects received all three treatments as planned. There was a total of 25 subjects who received Treatment A, 25 subjects who received Treatment B, and 25 subjects who received Treatment C. Two subjects missed period 2 dosing, with one subject missing Treatment A (Baclofen Oral Suspension, Fasted) and one subject missing Treatment B (Baclofen Oral Suspension, Fed). Two subjects discontinued prematurely from the study after receiving one treatment (one received Treatment A, and one subject received Treatment B)

Table 3 Exposure

Table 2.5-1. Exposure to Baclofen in Study RM 05-PK001 Safety Population				
		Baclofen Oral Suspension 5mg/mL (4 mL)		Baclofen Tablet USP 20 mg
		Fasted	Fed	Fasted
Parameter	Statistics	(N=25)	(N=25)	(N=25)
Number of subjects exposed to each treatment	n (%)	25 (100.0)	25 (100.0)	25 (100.0)

n (%) = number and percentage of subjects in the specified group; N = number of subjects in the specified population under each treatment; USP = United States Pharmacopoeia.
Baclofen Oral Suspension Fasted = Treatment A; Baclofen Oral Suspension Fed = Treatment B; Baclofen Tablet USP = Treatment C.
Source: Table 14.3.3 in Report RM-05-PK001.

Source: Sponsor

6.2. Safety Results

6.2.1. Deaths

None

6.2.2. Serious Adverse Events

None

6.2.3. Significant Adverse Events

Subject (b) (6) (a 31-year-old male) had two AEs which led to study discontinuation (increased creatinine, and increased blood creatine phosphokinase). Subject (b) (6) received only one treatment of the study drug, Treatment B, on (b) (6). The Investigator spoke with the subject on (b) (6), and subject was in no distress, had no urinary complaints, no anorexia or discomfort. Subject denied taking anabolic steroids, working out or taking any supplements. On physical exam, no costovertebral angle tenderness. Subject did not have any clinically significant findings in BUN or eGFR. Blood creatinine and creatinine phosphokinase levels are listed in the table below.

Table 4 Subject (b) (6) Blood Creatinine and Creatine Phosphokinase

Date	Blood Creatinine (mg/dL) (Normal range: 0.67-1.31)	Creatine Phosphokinase (U/L) (Normal range: 39-308)
(b) (6)	1.27	ND
	1.45	ND
	1.53	ND
	1.6	579
	1.45	746
	1.55	469
	1.47	220

Source: Sponsor

Reviewer comment:

The subject had mildly elevated blood creatinine level with peak value of 1.6. The CPK was noted to be elevated at on (b) (6); however, there was no baseline level for comparison. CPK return to within normal limits on (b) (6). There were no associated clinical signs or symptoms with the elevated creatinine or CPK. The adverse event does not appear to be clinically significant.

6.2.4. Treatment Emergent Adverse Events and Adverse Reactions

Table 5 Overview of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Treatment – Safety Population

System Organ Class Preferred Term	Baclofen Oral Suspension 5mg/mL (4mL) Fasted (N=25) n(%)	Baclofen Oral Suspension 5mg/mL (4mL) Fed (N=25) n(%)	Baclofen Tablet USP 20 mg Fasted (N=25) n(%)	All Subjects (N=27) n(%)
Subjects with at least One TEAE	2 (8.0)	3 (12.0)	2 (8.0)	5 (18.5)
Investigations	0 (0.0)	2 (8.0)	1 (4.0)	3 (11.1)
Blood creatine phosphokinase increased	0 (0.0)	1 (4.0)	0 (0.0)	1 (3.7)
Blood creatinine increased	0 (0.0)	1 (4.0)	0 (0.0)	1 (3.7)
Blood pressure increased	0 (0.0)	1 (4.0)	0 (0.0)	1 (3.7)
Urine analysis abnormal	0 (0.0)	0 (0.0)	1 (4.0)	1 (3.7)
Nervous system disorders	1 (4.0)	1 (4.0)	1 (4.0)	2 (7.4)
Somnolence	1 (4.0)	1 (4.0)	1 (4.0)	2 (7.4)
Eye disorders	0 (0.0)	0 (0.0)	1 (4.0)	1 (3.7)
Conjunctival hemorrhage	0 (0.0)	0 (0.0)	1 (4.0)	1 (3.7)
Musculoskeletal and connective tissue disorders	1 (4.0)	0 (0.0)	0 (0.0)	1 (3.7)
Back pain	1 (4.0)	0 (0.0)	0 (0.0)	1 (3.7)

Source: Sponsor

Reviewer Comment:

Aside from the adverse event of increased creatinine and CPK in one subject (refer to Section 6.3.3) which does not appear to be clinically significant, the adverse events are similar across treatment groups with somnolence being the most frequent. There were no adverse events related to the oral cavity, i.e. changes in oral mucosa.

6.2.5. **Laboratory Findings**

Hematology

There were no clinically significant findings or changes in hematology reported during the study.

Chemistry

Subject (b) (6) had clinically significant chemistry findings which led to subject discontinuation from the study, as described in Section 6.3.3. There were no clinically significant findings or changes in chemistry values

Urinalysis

There was one clinically significant urinalysis reported in the study. Subject (b) (6) had an abnormal urinalysis (bacteria in urine, assessed as mild in intensity) reported at the end of study visit. A repeat urinalysis was not conducted as subject was lost to follow up following several attempts to contact the subject to schedule the repeat urinalysis. A final certified letter was sent to subject on (b) (6) documenting that subject was considered lost to follow up.

6.2.6. **Vital Signs**

One subject (Subject (b) (6) experienced a TEAE of blood pressure increased following treatment with Baclofen Oral Suspension (fed) in period 1.

Following treatment with study drug, the subject's systolic blood pressure rose to a maximum value of 170 mmHg at an unscheduled timepoint approximately 2 hours post-dose, and the subject's diastolic blood pressure rose to a maximum of 92 mmHg at the 10-hour post-dose timepoint. The 12-hour and 24-hour post-dose time point blood pressure readings for this subject were 128/75 mmHg and 132/76 mmHg, respectively. Of note, the pre-dose blood pressure reading for this subject was 154/88 mmHg.

The TEAE of blood pressure increased was mild in severity, possibly related to study drug. There were no clinically significant signs or symptoms associated with the adverse event.

6.2.7. **Electrocardiograms (ECGs)**

There were no clinically significant ECG findings reported during the 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 suspension label.

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): Study RM-05-PK001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time		

<table>
<tr><td colspan="3">employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">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: _____</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☒</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☒</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

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/

SUSANNE R GOLDSTEIN
01/31/2022 04:48:51 PM

LAURA A JAWIDZIK
01/31/2022 08:33:32 PM