# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215422Orig1s000

# NON-CLINICAL REVIEW(S)

**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: | 215-422 |
| Supporting document: | 001 |
| Serial number: | 0001 |
| Applicant's letter date: | January 22, 2021 |
| CDER stamp date: | January 22, 2021 |
| Product: | LYVISPAH™ (Baclofen) |
| Indication: | Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity |
| Applicant: | Saol Therapeutics Research LTD |
| Clinical Review Division: | Division of Neurology 1 |
| Reviewer: | Richard Siarey |
| Supervisor: | Lois Freed |
| DN1 Director (acting): | Teresa Buracchio |
| Project Manager: | Taura Holmes |

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# 1 EXECUTIVE SUMMARY

## 1.1 Introduction

The sponsor has developed LYVISPAH™ (Baclofen oral granules) for treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity, with a recommended maximum dose of 20 mg four times a day.

## 1.2 Brief Discussion of Nonclinical Findings

The genetic toxicology studies (Ames and in vitro chromosomal aberration) assays were negative. However, there were issues with the characterization of the drug solutions used, which make the studies inadequate.

## 1.3 Recommendations

### 1.3.1 Approvability

The NDA was submitted as a 505(b)(2) application and relies on the nonclinical information obtained for LIORESAL® (NDA 17-851) with no additional nonclinical studies needed to support the NDA. Therefore, from a nonclinical perspective approval of NDA 215-422 is recommended.

### 1.3.3 Labeling

No additions to the nonclinical sections of labeling are recommended.

# 2 Drug Information

## 2.1 Drug

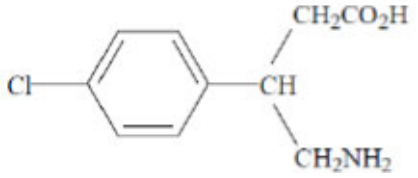
CAS Registry Number: 1134-47-0

Generic Name: Baclofen

Chemical Name: β-(Aminomethyl)-4-chlorobenzenepropanoic acid β -(Aminomethyl)-p-chlorohydrocinnamic acid (γ-amino-β-/p-chlorophenyl/-butanoic acid) β-(4-chlorophenyl) GABA

Molecular Formula/Molecular Weight: $C_{10}H_{12}ClNO_2$ / 213.7 g/mol

Structure or Biochemical Description: from the sponsor



Pharmacologic Class: GABA-ergic receptor agonist

### 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 140719 (DN1, treatment of spasticity).

### 2.3 Drug Formulation

LYVISPAH™ is formulated as a rapidly dissolving granule for oral administration.

### 2.4 Comments on Novel Excipients

There are no novel excipients used in the drug product; except for the strawberry flavor all excipients are compendial.

### 2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population for LYVISPAH™ are individuals with spasticity resulting from multiple sclerosis. An initial low oral dose is recommended, with 80 mg/day (20 mg four times a day) the recommended maximum dose.

### 2.7 Regulatory Background

A pre-IND WRO letter meeting for IND 140719 was sent on February 15, 2019, and the IND was received on July 8, 2020.

## 3 Studies Submitted

### 3.1 Studies Reviewed

Genetic Toxicology Studies

- Study №: 46528 (b) (4). Bacterial reverse mutation test.
- Study №: 46529 (b) (4). In vitro mammalian chromosome aberration test in cultured human lymphocytes.

# 7 Genetic Toxicology

## 7.1 In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

**Study title: Bacterial reverse mutation test**

| | |
|---|---|
| Study no.: | 46528 (b) (4) |
| Study report location: | EDR |
| GLP compliance: | Yes, OECD |
| QA statement: | Yes |
| Drug, lot #, and % purity: | Baclofen, Batch № 202101717m, 100% |

**Key Study Findings:** Baclofen was negative in the study.

**Methods**

| | |
|---|---|
| Strains: | TA98, TA100, TA102, TA1535, and TA1537 |
| Concentrations in definitive study: | 212.5, 625, 1250, 2500, and 5000 µg/plate |
| Basis of concentration selection: | Doses were selected form a preliminary study with TA98, TA100, and TA102 strains at a dose range of 10-5000 µg per plate |
| Negative control: | See table below. |
| Positive control: | See table below. |
| Formulation/Vehicle: | DMSO |
| Incubation & sampling time: | 37°C for 48-72 hours |
| Comment on Study Validity: | Five concentrations of baclofen were assayed in triplicate using the plate incorporation but see below. |

| | TA98 | TA100 | TA102 | TA1535 | TA1537 |
|---|---|---|---|---|---|
| **+ve control** | | | | | |
| Without S9 mix: | 2-NF 0.5 µg | NaAzide 1 µg | MMC 0.5 µg | NaAzide 1 µg | 9-AA 50 µg |
| With S9 mix*: | 2-AM 2 µg | B[a]P 5 µg | 2-AM 20 µg | 2-AM 2 µg | 2-AM 2 µg |
| **-ve control** | DMSO | DMSO | DMSO | DMSO | DMSO |

2-NF is 2-nitrofluorene, NaAzide is sodium azide, 9-AA is 9-aminoacridine, MMC is mitomycin C, B[a]P is benzo[a]pyrene, 2-AA is 2-anthramine. The liver S9 mix was prepared from rats treated with Aroclor 1254.

**Study validity**

The sponsor reported a drug substance issue, which was concerned with the density measurement of the test solution. In the assay, the density measurement of the test solution was too high (b) (4). The sponsor addressed this by preparing 3 new formulations of the test solution and measuring the density of these new solutions. The average density of the 3 new formulations was (b) (4), which is close to the estimated value of (b) (4). However, the original test solution was not retested for density, resulting in uncertainty about the characteristics of original solution.

**Results**

In the study, no precipitation of the assumed baclofen solution was observed up to 5000 µg/plate. No toxicity was observed up to 5000 µg/plate in any strain in the presence and absence of S9 mix. No increases in revertants were observed up to

5000 µg/plate. However, with the uncertainty in the characteristics of the baclofen solution it is not possible to know whether baclofen was tested and therefore, the validity of the assay.

## 7.2 In Vitro Assays in Mammalian Cells

**Study title: In vitro mammalian chromosome aberration test in cultured human lymphocytes**

| | |
|---|---|
| Study no.: | 46529 (b) (4) |
| Study report location: | EDR |
| GLP compliance: | Yes, OECD |
| QA statement: | Yes |
| Drug, lot #, and % purity: | Baclofen, Batch № 202101717m, 100% |

**Key Study Findings:** Baclofen at the highest dose tested (1 mM) induced chromosomal aberrations in human lymphocytes in the absence of S9 with 20-hour exposure compared to concurrent vehicle control but not compared to historical control.

**Methods**

| | |
|---|---|
| Cell line: | Human blood lymphocytes |
| Concentrations in definitive studies 3 hours absence & presence S9: 20 hours in absence of S9: | 0.0046, 0.0139, 0.0417, 0.125, 0.25, 0.5, and 1 mM |
| Basis of concentration selection: | Doses were selected from a preliminary study at a dose range of 0.0016-1 mM and the guideline for highest dose tested, of 1 mM |
| Negative control: | DMSO |
| Positive control: | 0.2 & 0.3 and 2 & 3 µg/mL Mitomycin C 12.5, and 25 µg/mL Cyclophosphamide |
| Formulation/Vehicle: | DMSO |
| Incubation & sampling time: | 3 and 20 hours in the absence of S9 and 3 hours in the presence of S9*; 37°C<br>* Aroclor 1254-induced rat liver S9 |
| Comment on Study Validity: | Three doses (0.25, 0.5, and 1 mM) were analyzed in at least duplicate in each treatment; 3- and 20-hours in the absence of S9 and 3-hours in the presence of S9 in 150 cells/duplicate and analysis was undertaken on 300 metaphases/dose level but see below. |

**Study validity**

The sponsor reported a substance issue, which was concerned with the density measurement of the test solution. In the assay, the density measurement of the test solution was too low (b) (4), below the density of DMSO (1.101 g/cm$^3$). The

sponsor addressed this issue by preparing 3 new formulations of the test solution and measuring the density of these new solutions. The average density of the 3 new formulations was (b) (4), which is close to the estimated value of (b) (4). However, the original test solution was not retested for density resulting in uncertainty about the characteristics of the original solution.

**Results**

In the definitive studies, no cytotoxicity was observed at any tested dose. No significant effects were observed up to 1 mM after 3-hour exposure in the absence of S9, although a slight increase in chromosomal aberrations at the lowest dose (0.25 mM) compared to control was noted. There was a statistically significant increase (3%) in the frequency of cells with chromosomal aberrations at the highest dose (1 mM) assessed after 20-hour exposure in the absence of S9. No significant effects were observed up to 1 mM after 3-hour exposure in the presence of S9. The decrease in mitotic index in the 20-hour treatment in the absence of S9 was 24% at 1 mM. Although increase in frequency of cells with chromosomal aberrations was statistically significant compared to concurrent vehicle control, the increase remained within the historical data range; the historical continuous treatment data has a negative control range (95% limits) of 0-3.5%. However, with the uncertainty in the characteristics of the baclofen solution it is not possible to know whether baclofen was tested and therefore, the validity of the assay.

**Tables: chromosome aberration data (Sponsors)**
**In absence of S-9 with 3-hour treatment**

| Doses mM | Slide Nb. | Nb. of cells scored | NA | Structural chromosome aberrations (type and number) | | | | | | | | | Cells with structural chromosome aberrations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | G | Chromatid | | Chromosome | | MA | PU | Total +G | Total -G | Nb. +G | Frequency (%) +G | Nb. -G | Frequency (%) -G |
| | | | | | D | Exch | D | Exch | | | | | | | | |
| 0 | 47 C1 | 150 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **2** | **2** | 1 | **0.7** | 1 | **0.7** |
| | 31 C2 | 150 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | | | 1 | | 1 | |
| 0.25 | 87 C1 | 150 | 0 | 0 | 1 | 0 | 4 | 0 | 0 | 0 | **7** | **7** | 4 | **2.0** | 4 | **2.0** |
| | 77 C2 | 150 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | | | 2 | | 2 | |
| 0.5 | 81 C1 | 150 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **2** | **2** | 0 | **0.7** | 0 | **0.7** |
| | 55 C2 | 150 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | | | 2 | | 2 | |
| 1 | 35 C1 | 150 | 2 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | **3** | **3** | 3 | **1.0** | 3 | **1.0** |
| | 69 C2 | 150 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | 0 | | 0 | |
| MMC 3 µg/mL | 49 C1 | 50 | 0 | 0 | 9 | 11 | 1 | 0 | 0 | 0 | **51** | **51** | 17 | **39.0** | 17 | **39.0** |
| | 57 C2 | 50 | 0 | 0 | 14 | 14 | 1 | 0 | 1 | 0 | | | 22 | | 22 | *** |

Nb.: number
NA: numerical aberrations, G: gap, D: deletion, Exch: exchange, MA: multiple aberrations, PU: pulverization.
C1: culture 1 (Female)
C2: culture 2 (Female)
0: vehicle control (DMSO)
MMC: Mitomycin C
Statistical analysis: $\chi^2$ test ***: $p < 0.001$ (performed only for cells with structural aberrations excluding gaps)

**In absence of S-9 with 20-hour treatment**

| Doses mM | Slide Nb. | Nb. of cells scored | NA | Structural chromosome aberrations (type and number) G | Chromatid D | Chromatid Exch | Chromosome D | Chromosome Exch | MA | PU | Total +G | Total -G | Cells with structural chromosome aberrations Nb. +G | Frequency (%) +G | Nb. -G | Frequency (%) -G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 52 C1 | 150 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | **2** | **2** | 1 | **0.7** | 1 | **0.7** |
| | 34 C2 | 150 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | | | 1 | | 1 | |
| 0.25 | 84 C1 | 150 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **2** | **2** | 1 | **0.7** | 1 | **0.7** |
| | 70 C2 | 150 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | | | 1 | | 1 | |
| 0.5 | 36 C1 | 150 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** | **1** | 0 | **0.3** | 0 | **0.3** |
| | 85 C2 | 150 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | | | 1 | | 1 | |
| 1 | 76 C1 | 150 | 0 | 0 | 4 | 0 | 2 | 0 | 0 | 0 | **11** | **11** | 5 | **3.0** | 5 | **3.0** |
| | 58 C2 | 150 | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 0 | | | 4 | | 4 | * |
| MMC | 64 C1 | 50 | 0 | 0 | 3 | 6 | 1 | 0 | 0 | 0 | **25** | **25** | 9 | **19.0** | 9 | **19.0** |
| 0.3 µg/mL | 40 C2 | 50 | 0 | 0 | 13 | 2 | 0 | 0 | 0 | 0 | | | 10 | | 10 | *** |

Nb.: number
NA: numerical aberrations, G: gap, D: deletion, Exch: exchange, MA: multiple aberrations, PU: pulverization.
C1: culture 1 (Female)
C2: culture 2 (Female)
0: vehicle control (DMSO)
MMC: Mitomycin C

Statistical analysis: $\chi^2$ test

*: $p < 0.05$ (performed only for cells with structural aberrations excluding gaps)
***: $p < 0.001$ (performed only for cells with structural aberrations excluding gaps)

**In presence of S-9 with 3-hour treatment**

| Doses mM | Slide Nb. | Nb. of cells scored | NA | Structural chromosome aberrations (type and number) | | | | | | | | | Cells with structural chromosome aberrations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | G | Chromatid | | Chromosome | | MA | PU | Total +G | Total -G | Nb. +G | Frequency (%) +G | Nb. -G | Frequency (%) -G |
| | | | | | D | Exch | D | Exch | | | | | | | | |
| 0 | 74 C1 | 150 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | **4** | **4** | 2 | **1.3** | 2 | **1.3** |
| | 42 C2 | 150 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | | | 2 | | 2 | |
| 0.25 | 65 C1 | 150 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** | **0** | 0 | **0.3** | 0 | **0.0** |
| | 38 C2 | 150 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | | | 1 | | 0 | |
| 0.5 | 30 C1 | 150 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **4** | **4** | 0 | **0.3** | 0 | **0.3** |
| | 54 C2 | 150 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | | | 1 | | 1 | |
| 1 | 79 C1 | 150 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | **0** | 0 | **0.0** | 0 | **0.0** |
| | 45 C2 | 150 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | 0 | | 0 | |
| CPA | 60 C1 | 50 | 0 | 0 | 16 | 1 | 2 | 0 | 2 | 0 | **50** | **50** | 16 | **37.0** | 16 | **37.0** |
| 25 µg/mL | 72 C2 | 50 | 0 | 0 | 22 | 4 | 3 | 0 | 0 | 0 | | | 21 | | 21 | *** |

Nb.: number
NA: numerical aberrations, G: gap, D: deletion, Exch: exchange, MA: multiple aberrations, PU: pulverization.
C1: culture 1 (Female)
C2: culture 2 (Female)
0: vehicle control (DMSO)
CPA: Cyclophosphamide
Statistical analysis: $\chi^2$ test ***: $p < 0.001$ (performed only for cells with structural aberrations excluding gaps)

**Table: Mitotic Index for 20-hour treatment in absence of S9 (Sponsors)**

| Doses mM | Slide Nb. | Mitotic index (%) | Mean Mitotic Index (%) | Mean Mitotic Index as % of the control | Decrease in Mitotic Index (%) |
|---|---|---|---|---|---|
| 0 | 52 C1 | 11.1 | 10.80 | 100 | |
| | 34 C2 | 10.5 | | | |
| 0.0046 | 43 C1 | 11.3 | 10.60 | 98 | 2 |
| | 63 C2 | 9.9 | | | |
| 0.0139 | 82 C1 | 10.5 | 10.20 | 94 | 6 |
| | 48 C2 | 9.9 | | | |
| 0.0417 | 33 C1 | 9.0 | 8.90 | 82 | 18 |
| | 78 C2 | 8.8 | | | |
| 0.125 | 59 C1 | 9.6 | 10.60 | 98 | 2 |
| | 41 C2 | 11.6 | | | |
| 0.25 | 84 C1 | 9.2 | 8.80 | 81 | 19 |
| | 70 C2 | 8.4 | | | |
| 0.5 | 36 C1 | 11.3 | 11.45 | 106 | none |
| | 85 C2 | 11.6 | | | |
| 1 | 76 C1 | 7.7 | 8.20 | 76 | 24 |
| | 58 C2 | 8.7 | | | |
| MMC 0.2 µg/mL | 53 C1 | 9.5 | 7.95 | 74 | 26 |
| | 75 C2 | 6.4 | | | |
| MMC 0.3 µg/mL | 64 C1 | 8.3 | 6.40 | 59 | 41 |
| | 40 C2 | 4.5 | | | |

Nb.: number
C1: culture 1 (Female)
C2: culture 2 (Female)
0: vehicle control (DMSO)
MMC: Mitomycin C

**Table: Historical data (Sponsors)**

| | Vehicle Control | | | | MMC (2 µg/mL) | | MMC (3 µg/mL) | | MMC (0.2 µg/mL) | | MMC (0.3 µg/mL) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment duration | Short treatment | | Continuous treatment | | Short treatment | | | | Continuous treatment | | | |
| Harvest time | 20 hours | | 20 hours | | 20 hours | | | | 20 hours | | | |
| Parameter | Mitotic index | % ab. cells | Mitotic index | % ab. cells | Mitotic index | % ab. cells | Mitotic index | % ab. cells | Mitotic index | % ab. cells | Mitotic index | % ab. cells |
| n | 26 | 24 | 26 | 24 | 26 | 21 | 26 | 3 | 26 | 16 | 26 | 8 |
| Mean | 12.6 | 1.1 | 9.1 | 1.2 | 3.6 | 43.7 | 2.8 | 28.6 | 5.9 | 24.9 | 4.9 | 23.6 |
| SD | 3.5 | 0.8 | 3.2 | 1.0 | 1.4 | 9.0 | 1.2 | 2.4 | 1.6 | 7.4 | 1.4 | 9.3 |
| Lower CL 95% | 11.2 | 0.7 | 7.8 | 0.8 | 3.0 | 39.6 | 2.3 | 22.8 | 5.3 | 21.0 | 4.3 | 15.8 |
| Upper CL 95% | 14.0 | 1.4 | 10.3 | 1.6 | 4.2 | 47.7 | 3.3 | 34.5 | 6.6 | 28.8 | 5.5 | 31.3 |
| $5^{th}$ Percentile | 8.3 | 0.0 | 3.9 | 0.0 | 2.0 | 28.0 | 1.3 | 25.9 | 3.2 | 13.0 | 3.0 | 11.0 |
| Median | 12.2 | 1.0 | 8.9 | 0.9 | 3.5 | 46.0 | 2.7 | 30.0 | 5.5 | 26.0 | 5.2 | 22.3 |
| $95^{th}$ Percentile | 18.9 | 2.0 | 13.2 | 3.0 | 5.4 | 56.0 | 4.9 | 30.0 | 8.6 | 35.0 | 7.5 | 37.0 |
| Min | 4.8 | 0.0 | 3.0 | 0.0 | 0.3 | 25.0 | 0.9 | 25.9 | 3.1 | 13.0 | 2.4 | 11.0 |
| Max | 21.1 | 4.0 | 15.6 | 3.5 | 7.5 | 57.0 | 5.3 | 30.0 | 9.5 | 35.0 | 7.8 | 37.0 |

# 11 Integrated Summary and Safety Evaluation

The sponsor conducted Ames and in vitro chromosomal aberration assays, although the Division informed the sponsor that additional nonclinical studies would not be needed (Pre-IND WRO letter February 15, 2019). The Ames assay was negative. In the chromosomal aberration assay, in the absence of S9 with 20-hour exposure there was a 3% increase in the frequency of cells compared to concurrent negative controls. However, the increased frequency was within the historical range of 0-3.5%.

The studies were not adequate as discrepancies were noted in the density of the test solution, which resulted in the uncertainty whether baclofen was tested or at what concentrations.

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RICHARD J SIAREY
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11/21/2021 06:13:56 PM
I concur.