STUDY REPORT

Efficacy Testing of AsCurin in Paclitaxel-induced Peripheral Neuropathic Pain in Male SD Rats.

STUDY NUMBER : 80-22-IPH

Client

HealthDoc LLC,
USA

TEST FACILITY

Animal pharmacology facility,
Biology division,
Aragen Life Sciences PVT., LTD.,
28 A, IDA, Nacharam,
Hyderabad 500 076,
India.

Phone No: +91-40-66281830
FAX NO: +91-40-66281505

INVESTIGATORS' DECLARATION

We, the undersigned, have prepared this report and hereby assure that the study was conducted in accordance with the approved protocol. We undertake that all the essential documents pertaining to this study will be archived for a period of 2 months.

Dr. Kumaran Dandapani,
Study Director

Date: 20 Feb. 23

Table of Contents

1.0 INTRODUCTION

Study Title	:	Efficacy Testing of AsCurin in Paclitaxel-induced Peripheral Neuropathic Pain in Male SD Rats.
Study Type	:	Efficacy study
Route of Administration	:	Per oral
Live Phase Duration including Acclimatization	:	35 Days
Test Facility	:	Aragen Life Sciences Private Limited, Biology Division, 28 a, IDA, Nacharam, Hyderabad 500 076 India
Schedule	:	Study Initiation: 25-12-2022 Experimental Starting Date: 25-12-2022 Acclimatization: 22-12-2022 In life phase Completion Date: 14-01-2023
Study Compliance	:	This study was conducted as per the mutually agreed study plan and the Aragen Life Sciences Standard Operating Procedures.
Amendment & Deviation	:	During the study period there was no amendment and deviation were raised.
Archive	:	Soft copies of study plan, data and study report will be archived for the periods of two months.

2.0 OBJECTIVE

To assess the efficacy of AsCurin in Paclitaxel-induced Peripheral Neuropathic Pain in male SD Rats.

3.0 MATERIALS AND METHODS

3.1 Test System

Species Strain and Sex	:	Rat (Sprague Dawley), male

Justification for selection of species	:	Rats are used as per Flatters SJL, et al., 2006.
Justification for route of administration Body weight	: :	This the intended route in clinics 200-250 grams
No. of groups No. of rats/dose	: :	4 G1 – 8 rats (Saline) G2 – 8 rats (Paclitaxel + Vehicle) G3 – 8 rats (Paclitaxel + Gabapentin) G4 – 8 rats (Paclitaxel + AsCurin)
Total no of animals	:	32 rats
Identification	:	The identification was done with tail marking (by permanent marker).
Acclimatization	:	After examination for good health and the suitability for the study, the rats were acclimatized at least for three days before start of the study. During acclimatization animals were observed twice daily.

3.2 Group allocation

Group	Treatment	# Rats	Dose			Route of Administration
			(mg/kg)	Conc. (mg/mL)	Vol. (mL/kg)	
1	Vehicle + Milli Q Water	8	-	-	10	*p.o.*
2	Paclitaxel + Milli Q Water	8	-	-	10	*p.o.*
3	Paclitaxel + Gabapentin	8	100	10	10	*p.o.*
4	Paclitaxel + AsCurin	8	500*	1	10	*p.o.*
* indicate human dose and with which a rat dose was derived as reported by Nair and Jacob,2016						

3.3 Husbandry

Two to three rats per cage were housed in standard poly-sulfone cages with stainless steel top grill having facilities for pelleted food and polycarbonate drinking water bottle with stainless steel sipper tubes. Rats were provided with clean & sterilized corn cob as bedding.

Animals were maintained and monitored for good health in accordance with the Test facility SOPs and at the discretion of the laboratory animal veterinarian. Certified rodent diet was provided ad libitum. Water was available ad libitum. Periodic analysis of the water was performed, and the results are archived at the test facility. Environmental controls for the animal room were set to maintain a temperature of 22 to 25°C, humidity of 30-70% RH, and a 12-h light/12-h dark cycle.

3.4 Test Item Information

Test Item	:	AsCurin
Supplied by (Name and Address)	:	HealthDoc LLC
Recommended Storage Condition	:	2-8°C
Reference Item	:	Gabapentin
Lot No.	:	JGHAH
Molecular weight	:	171.24
Purity	:	>98%
Recommended Storage Condition	:	2-8°C

3.5 Personal Protective Equipment

Personal Protective Equipment (PPE) like safety goggles, hand gloves, face mask, head cap and apron were used wherever applicable.

3.6 Dose Formulation

Paclitaxel formulation: (Section 11.1)

Paclitaxel (Hetero Healthcare Ltd, 100 mg in 16.70 mL) was formulated in Vehicle: 2 parts of 0.9% saline and 1 part of 1:1 ratio of cremophor EL: Ethanol.

AsCurin in Formulation: (Section 11.2)

Required quantity of AsCurin was weighed and dissolved in Milli Q water every day before dosing.

Gabapentin Formulation: (Section 11.3)

Appropriate amount of Gabapentin was weighed and dissolved in saline on the day of dosing.

3.7 Dose Volume

Dose volume of Gabapentin – 10 mL/kg

Dose volume of AsCurin – 10 mL/kg

3.8 Treatment

Based on body weight and basal pain readouts, rats were randomly assigned into above treatment groups as mentioned in Section 3.2 (Group Allocation).

- Group-1 was administered with Milli Q water
- Group- 2 was administered with Milli Q water
- Group-3 was administered with Gabapentin, 100 mg/kg, p.o.
- Group-4 animals were dosed with test compound – AsCurin, 500 mg human dose, p.o., i.e 5.16 mg*/100 gm of rat and dose was adjusted according to the body weight on the day of dosing-100mg of active ingredient was present in 1300 mg of test material (*Animal equivalent dose).

Post-dose rats from all the above groups were subjected to pain assessment on day 13, 15 and 18. Study and treatment was performed from day 13 to 18, a care was taken that all the treatment groups were present on each day of testing.

3.9 Pain Assessment

The male SD rats were habituated for 60 min and 30 min in the experimental room and plexiglass chambers respectively consecutively for 3 days. The paw withdrawal threshold (PWT) was measured for each rat before paclitaxel or saline injection, and it was used as basal PWT.

Neuropathic pain in rats were induced with the administration of paclitaxel (Hetero Healthcare Ltd, 100 mg), 2 mg/kg intra-peritoneal on days 0, 2, 4 and 6 at a final cumulative dose of 8 mg/kg (Group 2-4), except for those in the (Group 1) saline control group (Li, et al., 2017; Kim, et al., 2015). The injection was given through

intraperitoneal route (i.p.) for paclitaxel under the same experimental conditions. Baseline tactile allodynia/sensitivity to calibrated manual von Frey filaments was evaluated by using Dixon's up-and-down method on both hind paws. Based on 50% paw withdrawal threshold, rats were randomized into the above groups. Rats in group 1, 2 & 4 were dosed with the respective treatments, from day 13 through 18 post-paclitaxel administration. Group 3 rats were administered with gabapentin only on day 13, 15 & 18 before pain assessment. The paw withdrawal threshold for all the groups were recorded before and after treatment on day 13 (at 1, 3 & 5h post-treatment), 15 (at 3* or $5^{\#}$h post-treatment) & 18 (at 3* or $5^{\#}$h post-treatment), symbols * indicates testing timepoint for gabapentin, vehicle treatment groups $^{\#}$ indicates testing time point for AsCurin group.

Tactile Allodynia Testing: In order to evaluate the neuropathic pain, the baseline tactile sensitivity was evaluated on Day 13. The rats that were exhibiting 50% paw withdrawal threshold (50% PWT) ≤5g in the baseline test (BL) were utilized for further testing (T). These rats were randomly assigned to one of the above groups (with n=8 per group).

The paw withdrawal threshold was determined by increasing and decreasing stimulus intensity and calculated using Dixon's up-down method. The filament (maximum force of 15.0 g) was held in place for 6 s or until there was a withdrawal response.

Data was reported and plotted as 50 % PWT (g) threshold values. The experimenter was blinded to the drug treatment for all studies.

After completing the pain assessment, under mild gaseous anaesthesia, blood was collected from group 4 from all animals at 5.5h (i.e., after the last time point of pain assessment) post treatment and separated plasma was stored at -80°C to check the terminal compound levels in plasma; followed by euthanasia and collection of stomach for gross pathology (Bhattamisra et al., 2019) and histopathology examination (Simões S et al., 2019) by a pathologist who was blinded to the treatment groups.

3.10 Body Weights

Animals were weighed from the day of paclitaxel dosing and daily up to end of study.

3.11 Histopathology

After completion of pain assessment in paclitaxel-induced neuropathy model, normal, disease control and AsCurin group of rats will be euthanized under excessive CO2 asphyxia. Following euthanasia, stomach sacs will be collected, opened along the

greater curvature, and rinsed with cold normal saline, examined of gross lesions. The ulcer crater of each stomach will be sectioned out and fixed overnight in 10% neutral buffered formalin. A stomach tissue with ulcer carter will be sectioned (5-µm), stained with hematoxylin and eosin (H & E) and examined under a light microscope for histological and mucosal evaluations.

Microscopically, H&E tissues will be reported - a normal appearance, mild infiltrates of inflammatory cells into the lamina propria mucosa, with either no or only shallow erosion, or deep erosion and ulceration.

3.12 Disposal of Animals

After completion of experiment animals were euthanized under CO_2 asphyxiation as per SOP-BIO-IPH-126 and were disposed as per SOP-BIO-IPH-117.

4.0 ETHICAL CONSIDERATIONS

The protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) number: B113.

5.0 DATA HANDLING & RECORD KEEPING

All the data generated during the conduct of the study was directly entered into the respective raw data recording forms. The computer-generated data was also treated as raw data. All raw data and transcribed data forms were compiled by the study personnel.

6.0 REPORT

On completion of the experiment, a softcopy of the draft report is prepared in Aragen report format and will be submitted to the sponsor. Any comments/suggestions/modifications in the draft report will be incorporated within one month of the submission of the draft report. After incorporating the sponsor suggestions, a final report will be prepared, and electronic copies of the report (PDF /Word formats) will be submitted to the sponsor.

7.0 DISPOSAL OF TEST ITEM(S) AND STUDY SAMPLES

After submitting the final report, the left-over test item(s) and study samples will be discarded.

8.0 DATA MANAGEMENT AND ARCHIVING

Electronic raw data and analysis files were kept in the designated folders.

9.0 DATA CONFIDENTIALITY

All the data generated in connection with this study were kept confidential and were accessible only to the study personnel, sponsor and if necessary, to the IAEC of Aragen Life Sciences, Pvt. Ltd.

10.0 RESULTS

10.1 Temporal Effect of AsCurin on Paclitaxel-induced Tactile Allodynia

Rats which were injected with paclitaxel exhibited sustained pain response from day 13 to 18 revealed by significant decrease in paw withdrawal threshold as compared to normal vehicle group (Group-1), Following treatment from day 13 to 18 with AsCurin exhibited a significant increase ($p<0.001$) in paw withdrawal threshold as compared with paclitaxel + vehicle treated group (Group-2) at 1, 3 and 5h on day 13 post treatment. The time course efficacy study reveals that AsCurin treatment showed a maximum pain reversal at 5h post-treatment and based on this observation, subsequent pain testing on day 15 and 18 was performed at 5h post-dose. Group-3 rats administered with Gabapentin, 100 mg/kg on day 13, 15 and 18 (at 3h) had demonstrated a significant ($p<0.001$) reversal of tactile allodynia.

10.2 Gross pathology and Histology

Following vehicle (group 1; normal control & group 2; Paclitaxel + Vehicle) and AsCurin (group 4; Paclitaxel + AsCurin) 500mg HD (human dose) treatment from day 13 to 18, rats were euthanized and their stomach was collected. Terminal gross pathology observation reveals that neither vehicle (Group 1 & 2) nor AsCurin treated rats (Group 4) showed any ulcer related lesions in stomach. Further, H&E staining of stomach sections reveals that normal control, Paclitaxel + Vehicle and

Paclitaxel + AsCurin treated rats showed no evidence of sub mucosal oedema, inflammation, hemorrhage and mucosal erosion.

10.3 Gross pathology Findings

Sl.No	A.No	Group	Gross Ulcer Score
1	6	Normal	0
2	28		0
3	29		0
4	2		0
5	55		0
6	64		0
7	23		0
8	26		0
9	50		0
10	3	Pac+Vehicle	0
11	13		0
12	19		0
13	11		0
14	17		0
15	46		0
16	10		0
17	16		0
18	4	Pac+AsCurin (500 mg HD)	0
19	14		0
20	33		0
21	43		0
22	44		0
23	47		0
24	34		0
25	37		0
*HD-Human Dose, Pac-Paclitaxel			

10.4 Histopathology score

80-22-IPH Histopathology Score						
Group	**Animal No.**	**Observations**				**Total**
		Sub mucosal Oedema	**Inflammation**	**Haemorrhage**	**Mucosal erosion**	
Normal	6	0	0	0	0	0
	28	0	0	0	0	0
	29	0	0	0	0	0
	2	0	0	0	0	0
	55	0	0	0	0	0
	64	0	0	0	0	0
	23	0	0	0	0	0
	26	0	0	0	0	0
	50	0	0	0	0	0
	Mean	0	0	0	0	0
Pac+Vehicle	3	0	0	0	0	0
	13	0	0	0	0	0
	19	0	0	0	0	0
	11	0	0	0	0	0
	17	0	0	0	0	0
	46	0	0	0	0	0
	10	0	0	0	0	0
	16	0	0	0	0	0
	Mean	0	0	0	0	0
Pac+AsCurin (500 mg HD)	4	0	0	0	0	0
	14	0	0	0	0	0
	33	0	0	0	0	0
	43	0	0	0	0	0
	44	0	0	0	0	0
	47	0	0	0	0	0
	34	0	0	0	0	0
	37	0	0	0	0	0
	Mean	0	0	0	0	0

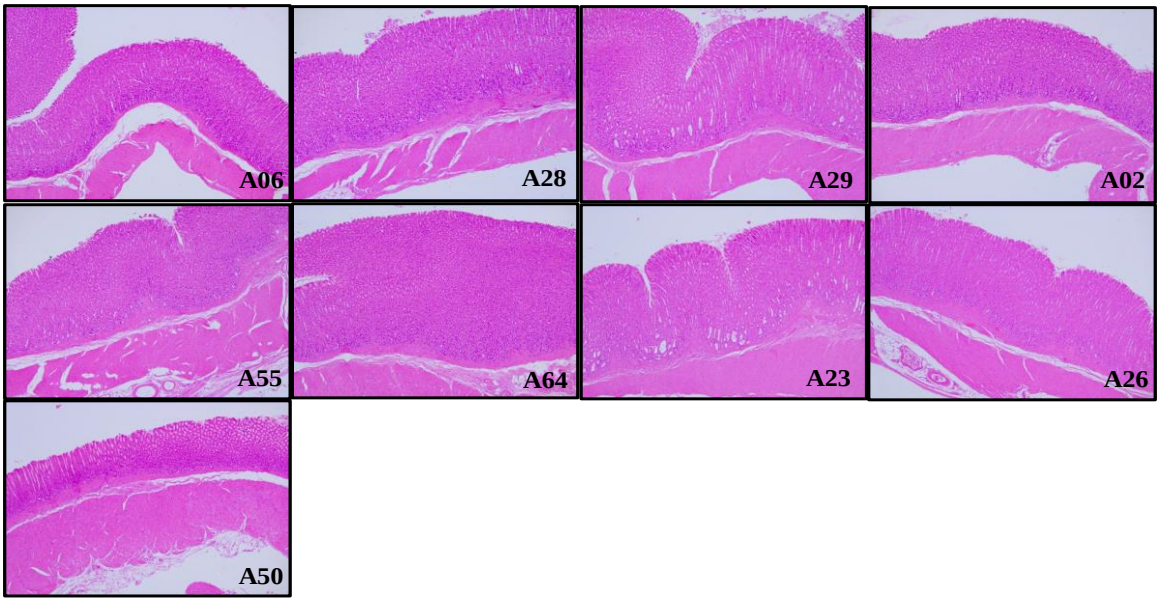
Key:

Sub mucosal edema: 0- Normal, 1-Mild, 2-Moderate, 3-Marked and 4-Severe
Inflammation: 0- Normal, 1-Mild, 2-Moderate and 3-Severe
Hemorrhage: 0- Normal, 1-Mild, 2-Moderate, 3-Marked and 4-Severe
Mucosal erosion: 0- Normal, 1-Minimal, 2-Mild and 3-Severe

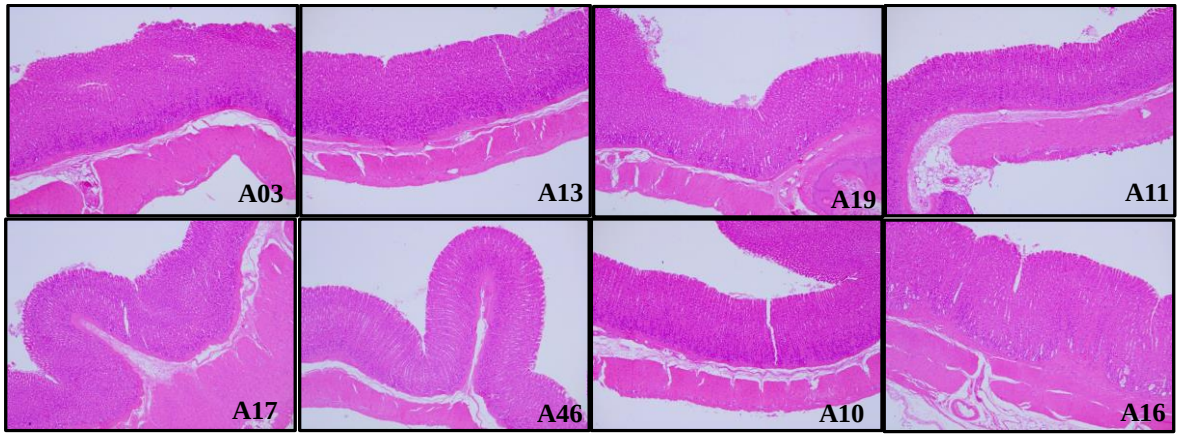
Pac-Paclitaxel, HD-Human dose

10.5 Hematoxylin & Eosin Staining Images

Group 1 - Normal + Vehicle



Group 2 – Paclitaxel + Vehicle



Group 4 – Paclitaxel + AsCurin 500mg HD (human dose)

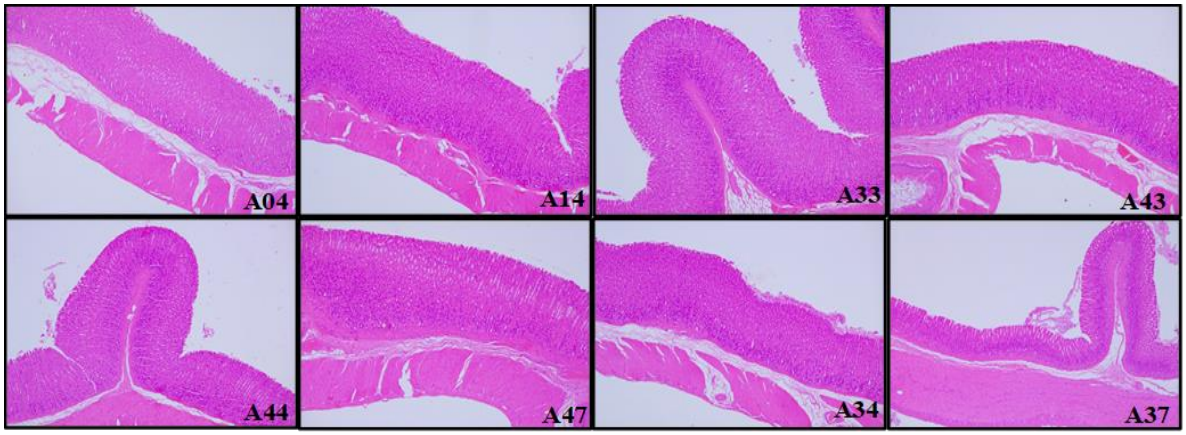
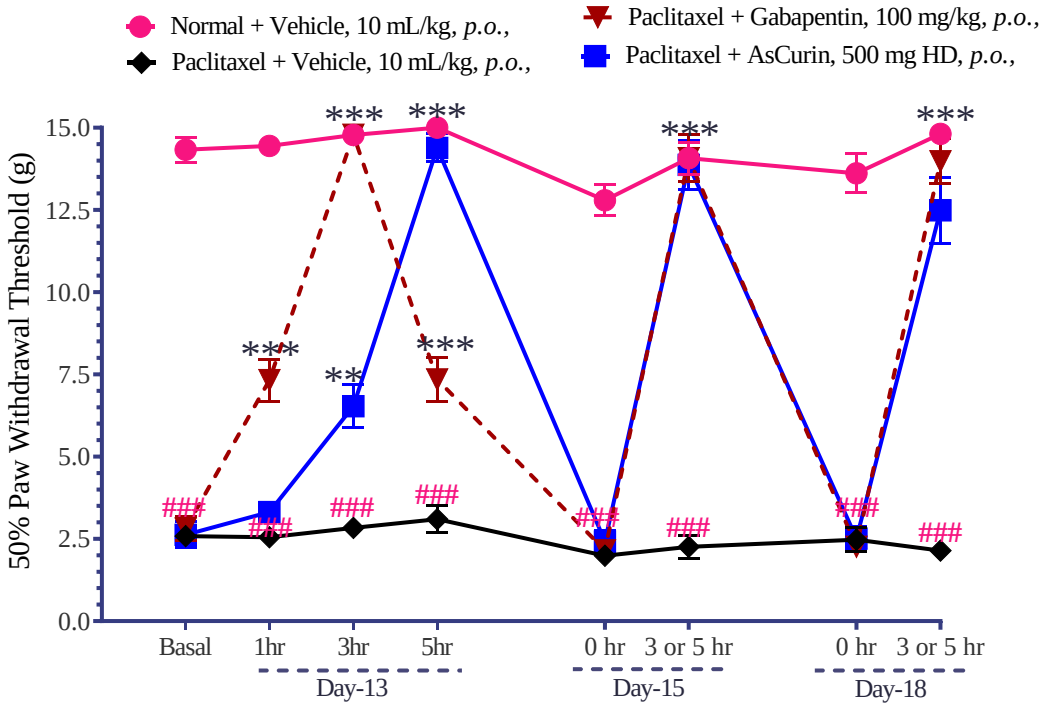


Figure-1. Temporal Evaluation of Effect of AsCurin on Paclitaxel-induced Tactile Allodynia in Male SD Rats



Data indicates Mean ± SEM, ###p<0.001 Vs Normal + Vehicle, ***p<0.001 Vs Paclitaxel + Vehicle. Two-way ANOVA followed by Dunnett's multiple comparisons test. n=8.
HD – human dose

10.6 Sorted Data of All Groups 50% Paw Withdrawal Threshold (g) (PWT)

Compiled Data									
Sl.No	A.No	Group	50% Paw Withdrawal Threshold							
			Day 13				Day 15		Day 18	
			0h	1h	3h	5h	0h	3/5h	0h	3/5h
1	6	Normal	13.3	15.0	15.0	15.0	13.3	15.0	10.8	15.0
2	28		15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
3	29		15.0	15.0	15.0	15.0	11.7	15.0	15.0	15.0
4	2		15.0	15.0	15.0	15.0	11.7	11.7	11.7	15.0
5	55		15.0	12.7	15.0	15.0	11.7	13.3	13.3	15.0
6	64		14.0	15.0	14.0	15.0	11.7	15.0	11.7	13.3
7	23		11.7	14.0	14.0	15.0	11.7	11.7	15.0	15.0
8	26		15.0	13.3	15.0	15.0	13.3	15.0	15.0	15.0
9	50		15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Mean			14.3	14.4	14.8	15.0	12.8	14.1	13.6	14.8
SEM			0.4	0.3	0.2	0.0	0.5	0.5	0.6	0.2
Count			9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
10	3	Pac+Vehicle	2.4	2.3	2.6	2.0	2.2	3.0	2.9	2.3
11	13		3.3	1.6	2.3	2.2	0.9	0.8	1.3	1.2
12	19		2.4	2.1	2.1	2.4	1.8	2.4	1.4	2.6
13	11		3.1	3.0	3.0	4.5	2.1	2.8	4.3	2.5
14	17		2.4	2.6	3.2	3.5	2.3	2.6	3.1	2.8
15	46		3.0	2.7	3.2	4.6	2.4	1.3	2.3	2.4
16	10		1.7	2.8	3.0	3.2	1.2	1.5	1.7	1.0
17	16		2.4	3.3	3.3	3.3	3.0	3.7	2.8	2.4
Mean			2.6	2.5	2.8	3.2	2.0	2.3	2.5	2.1
SEM			0.2	0.2	0.2	0.3	0.2	0.3	0.4	0.2
Count			8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
18	32	Pac+Gabapentin (100 mg/kg)	2.8	6.1	15.0	4.9	2.6	15.0	2.3	15.0
19	36		2.4	11.4	15.0	6.6	3.8	15.0	2.3	15.0
20	8		3.2	6.3	13.3	8.2	2.1	15.0	1.7	11.7
21	25		5.0	8.4	15.0	8.8	2.3	15.0	2.3	15.0
22	41		1.6	6.5	15.0	5.5	1.0	13.3	2.0	10.1
23	49		1.8	7.1	15.0	7.0	1.8	15.0	2.3	15.0
24	51		2.9	6.4	15.0	10.9	2.2	15.0	2.8	15.0
25	52		2.8	6.4	15.0	6.9	1.4	9.3	2.3	15.0
Mean			2.8	7.3	14.8	7.4	2.1	14.1	2.3	14.0
SEM			0.4	0.6	0.2	0.7	0.3	0.7	0.1	0.7
Count			8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
26	4	Pac+AsCurin (500 mg HD)	2.0	1.7	4.0	11.8	0.9	10.9	1.0	6.5
27	14		3.1	3.6	10.3	15.0	1.2	15.0	1.7	11.7
28	33		1.7	3.2	6.6	15.0	2.9	15.0	3.3	15.0
29	43		3.6	2.9	7.3	15.0	2.3	15.0	3.6	15.0
30	44		2.6	3.2	6.4	15.0	2.8	15.0	3.1	11.7
31	47		4.7	4.0	7.0	15.0	3.5	15.0	3.7	15.0
32	34		1.4	3.7	5.3	15.0	2.4	10.1	1.7	11.7
33	37		1.9	4.2	5.1	13.3	3.4	15.0	2.0	13.3
Mean			2.6	3.3	6.5	14.4	2.4	13.9	2.5	12.5
SEM			0.4	0.3	0.7	0.4	0.3	0.7	0.4	1.0
Count			8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
*HD-Human Dose, Pac-Paclitaxel										

11.0 TABLES

11.1 Dose formulation of Paclitaxel

Paclitaxel Formulation (Dose: 2mg/kg, Dose Vol: 2ml/kg i.p.,)													
		Paclitaxel stock (6mg/ml vial concentration)				Paclitaxel required concentration (1 mg/ml)							
Batch	Days	Vial (mg)	Vial Vol (ml)	Stock Conc. (mg)	Stock Conc. (mL)	No.of.animals	Average Body weight of each animal (gms)	Total weight (gms)	Pac. Dose (mg/kg)	Tot. amount of Pac. required (mg)	Tot. Vehicle vol required (1 mg/ml)	Tot. Pac Vol required (from vial - ml)	Tot. Vehicle Vol required (ml)
Batch 1	Day 0	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 2	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 4	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 6	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
Batch 2	Day 0	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 2	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 4	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 6	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
Batch 3	Day 0	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 2	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 4	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5
	Day 6	100.0	16.7	6.0	1.0	13.0	300.0	3900.0	2.0	7.8	7.8	1.3	6.5

11.2 Dose formulation of AsCurin

AsCurin (Dose: 500mg human dose; AED Active comp: 51.646 mg/kg; AED Actual comp: 671.3 mg/kg; Dose volume: 10 ml/kg; Con-5.1646 mg/ml)				
Day	Active Compound (mg)	Compound Weighed (mg)	Vehicle vol (ml)	Actual con (mg/ml)
07-01-2023	61.98	805.56	12.00	5.16
08-01-2023	92.96	1208.34	18.00	5.16
09-01-2023	123.95	1611.12	24.00	5.16
10-01-2023	123.95	1611.12	24.00	5.16
11-01-2023	123.95	1611.12	24.00	5.16
12-01-2023	139.44	1812.51	27.00	5.16
13-01-2023	92.96	1208.34	18.00	5.16
14-01-2023	30.99	402.78	6.00	5.16
*AED-Animal Equivalent Dose				

11.3 Dose formulation of Gabapentin

Gabapentin (Dose: 100 mg/kg; Dose volume: 10 ml/kg)						
Day	Stock Conc. (mg/mL)	Weighed (mg)	% Purity	Net Compound	Tot. Vehicle (mL)	Final Conc. (mg/mL)
Day 13	10.00	100.75	98.00	98.735	9.874	10.00
Day 15	10.00	100.75	98.00	98.735	9.874	10.00
Day 18	10.00	100.75	98.00	98.735	9.874	10.00

12.0 OBSERVATIONS

- Male SD rats injected with paclitaxel, 2 mg/kg/day injections on four alternate days (in total 8 mg/kg dose was administered to each rat) had exhibited a tactile allodynia on from day 13 to 18, as revealed by significant decrease in paw withdrawal threshold in comparison to normal vehicle group.
- Gabapentin 100 mg/kg treatment on day 13, 15 and 18 significantly reversed the tactile allodynia at 1, 3 and 5h, 3h & 3h post-dose respectively in comparison to paclitaxel + vehicle treatment.
- Continuous treatment with AsCurin, 500 mg human dose for 6 days increased the paw withdrawal threshold, and a significant effect was evidenced on day 13 (at 1, 3 & 5h), day 15 (at 5h) and day 18 (at 5h).
- Terminal gross pathology observation reveals that there is no ulcer lesion related changes in stomach of any of the treatment groups.
- Further H&E staining reveals that there was no evidence of ulceration in the stomach sections of any of the treatment groups.

13.0 REFERENCES:

1. Flatters SJL, Bennett GJ. Paclitaxel-induced painful peripheral neuropathy: the search for pathophysiology. Society of Neurosci Abstracts 2004b:982.2.
2. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016 Mar;7(2):27-31.
3. Kim HK, Kwon JY, Yoo C, Abdi S. The analgesic effect of rolipram, a phosphodiesterase 4 inhibitor, on chemotherapy-induced neuropathic pain in rats. Anesth Analg. 2015; 121:822–8.
4. Bhattamisra SK, Hooi LP, Shyan LP, Chieh LB, Candasamy M, Sahu PS. Effect of geraniol and clarithromycin combination against gastric ulcers induced by acetic acid and Helicobacter pylori in rats. Pharmacognosy Research. 2019;11(4).
5. Simões S, Lopes R, Campos MC, Marruz MJ, da Cruz ME, Corvo L. Animal models of acute gastric mucosal injury: Macroscopic and microscopic evaluation. Animal models and experimental medicine. 2019 Jun;2(2):121-6