FINAL REPORT
(Version #1)

EVALUATION OF THE EFFECT OF GB-67B IN CFA INDUCED ARTHRITIS IN RATS

STUDY No.

MD-31-012-0013

Prepared for:

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DATA PAGE

Study protocol signed by the Study Director:	12-Aug-2007
Induction of AIA:	13-Aug-2007
Completion of In-Life Phase:	10-Sep-2007
Preliminary Data	12-Sep-2007
Draft Report Date	23-Oct-2007
MD Biosciences Study Reference:	MD-31-012-0013
Sponsor:	Emory University
Contact:	Gregory Bluemling
Study Organization and Consultation:	MD Biosciences Div. of Morwell Diagnostics GmbH Gewerbestrasse 9, Postfach 8132 Egg b, Zurich Switzerland
Contact Person:	Amy Clausen
Testing Facility:	MD Biosciences Neurology Discovery Services Sheba-Tel Hashomer Hospital Ramat Gan, Israel
Collaborating Staff Members:	Carmit Kedar, Scientist Alejandro Reichstein, Technician Iren Gross, QA
Study Director:	Sigal Meilin, PhD
Date:	September 2007

1. SUMMARY:

Study Procedure and Aim: The aim of the present study was to evaluate the effect of GB-67B administered PO, in CFA induced arthritis in rats. Arthritis was induced by SC injection of CFA to the tail on study day 0. Dexamethasone, the positive control in this study was administered IP once daily from day 0 to day 28, the day of study termination. TIs were all administered once daily PO from study day 0 to study day 28.
Animal weight, Arthritis (AR) clinical score and paw volume were measured 3 times a week.

Body Weight:. Vehicle treated animals gained 15% of body weight and TI treated animals gained about 21% of body weight during 28 days, the entire study period. Group 4F, Dexamethasone treated animals gained only 2% body weight - this phenomenon was common.

Arthritis Clinical Score: No disease signs were noticed in any of the animals participated in the study **until study day 12**. On study day 12, 3 out of 10 animals of the vehicle were ill, expressing disease in several joints. The disease severity increased during the remaining study period and on study day 28, 7 out of 10 vehicle treated animals showed a significant disease expressed as multi joints welling and inflammation in more that one paw. Dexamethasone, the positive control in this study, at a dose of 1 mg/kg administered IP starting on day of study commencement prevented disease development completely (Mean Clinical Score on day 28: Vehicle treated group (1F): 1.5±0.4; Dexamethasone treated group (4F): 0.0±0.0; $p<0.01$ vs. vehicle treated group).
GB-67B administered at a dose of 30 mg/kg PO starting on study day 0 (groups 3F) was slightly active in reducing disease signs. Clinical Score on study day 28 for group 3F of GB-67B, was 0.9±0.4 $p<0.05$).

Paw Volume: Mean animal paw volume as measured by the Plethysmometer increased during the 28 days of the study by 77±11% in the vehicle treated animals (Group 1F). Dexamethasone treatment (Group 4F) completely prevented this increase in paw volume. On study day 28 the mean paw volume of the Dexamethasone treated animals was only 0.2±0.7% higher than baseline. GB-67B reduced paw volume in a dose related manner, whereas the highest dose tested in this study reduced paw volume by 50%.

2. OBJECTIVE:

To evaluate the anti-arthritic activity of GB-67B in adjuvant induced arthritis in rats.

3. REGULATORY/GUIDELINES:

This study did not follow any specific guideline.

4. ARCHIVING:

The following records are stored in the archives of MD Biosciences in Israel according to the GLP regulations for a period of 2 years:

- a copy of the final report,
- the study protocol and a documentation of all raw data and specimens generated during the conduct of the study
- the correspondence with the Sponsor concerning the study.

5. TEST MATERIALS:

5.1 Test Items:

Characterization and handling of each Test Item was under the responsibility of the Sponsor.

5.2 Identification, Storage and Handling of Experimental Items:

5.2.1 Test Item Vehicle control: DMSO and β-Cyclodextrin 98%

5.2.2 Test Item:

Name:	Triptolide Analogue GB-67B
Batch No.:	In final report
Supplied by:	Sponsor
Storage Conditions:	- 20 ºC
Expiry Date :	January 2008
Expiry Date (dosing solution):	October 2007

5.2.3 Test Item Positive Control:

Name:	Dexamethasone
Cat No.:	D1756
Lot No.:	035K1171
Supplied by:	Sigma
Storage Conditions:	4 °C - 8°C
Expiry Date:	April 2008

5.2.4 Induction Items:

Name:	Complete Freund's Adjuvant (CFA) 20 mg/ml
Cat No.:	IMAD-20
Supplied by:	MD Biosciences Division of Morwell Diagnostics GmbH
Character. & Physical State:	Mineral oil, containing heat killed *Mycobacterium Tuberculosis* H37 Ra at a concentration of 3 mg/ml
Storage Conditions:	2-8 ºC and protected from light following receipt until the time of use
Expiry Date:	2008

5.3 Preparation of Test Materials:

5.3.1 Test Items:

As dictated by the Sponsor and unless decided otherwise, test items were prepared prior to use as follows: TI was dissolved in DMSO to a concentration of 160mg/ml. Then 45% **β** -cyclodextrin solution was added (in water) to achieve a concentration of 32 mg/ml. Volume was administered according to doses.

5.3.2. Test Materials: (CFA)

A 20 mg/ml CFA solution was supplied by MD Biosciences and required no further preparations.

6. TEST SYSTEM:

6.1 Species/Strain: Rat / Lewis

6.2 Source: Harlan Laboratories, Israel

6.3 Gender: Female

6.4 Total No. of Animals: *n=44*

6.5 Age: Young adults, 200-220g at the study initiation.

6.6 Body Weight: Weight variation of animals at the time of treatment initiation had not exceeded ± 20% of the mean weight.

6.7 Animals Health: The health status of the animals used in this study was examined on arrival. Only animals in good health were acclimatized to laboratory conditions and were used in the study.

6.8 Acclimation: At least 5 days.

6.9 Housing: During acclimation and throughout the entire study duration, animals were housed within a limited access rodent facility and were kept in groups of maximum 5 mice in polypropylene cages (42.5 × 26.6 × 18.5 cm), fitted with solid bottoms and filled with wood shavings as bedding material.

6.10 Food and Water: Animals were provided with *ad libitum*- a commercial rodent diet and free access to drinking water, supplied to each cage via polyethylene bottles with stainless steel sipper tubes.

6.11 Environment: Automatically controlled environmental conditions were set to maintain temperature at 20-24°C with a relative humidity (RH) of 30-70%, a 12:12 hour light:dark cycle and 15-30 air changes/h in the study room. Temperature and RH were monitored daily.

6.12 Identification: Animals were given a unique animal identification tail mark. This number also appeared on a cage card, visible on the front of each cage. The cage card also contained the study and group numbers, route of administration, gender, strain and all other relevant details as to the treatment group.

6.13 Randomization: During the acclimation period, animals were randomly assigned to experimental groups according to a Table of Random Numbers.

6.14 Termination: At the end of the study, surviving animals were euthanized by CO_2 asphyxiation.

6.15 Justification: The rat had been selected since it represented the species of choice for this experimental animal model.

7. CONSTITUTION OF TEST GROUPS AND DOSE LEVELS:

The table below lists 4 experimental groups comprising the study:

Group No. & Gender	Group Size	Test Materials	Route	Dose Level (mg/kg)	Treatment regime
1F	10	DMSO	PO	0	Once daily
2F	11	GB-67B	PO	10	Once daily
3F	11	GB-67B	PO	30	Once daily
4F	11	Dexamethasone	IP	1	Once daily

8. TEST PROCEDURE

8.1 Induction of disease:

Animals were injected with 0.1 ml of 20% CFA into the tail base.

8.2 Treatment:

Rats were administered with test articles according to table at section 7.

8.3 Justification for Routes of Administration and Doses:

The Sponsor had selected all the above-mentioned routes of administration as the suitable routes applied at the current study and the specified doses (see also under Section 7).

9. EXAMINATIONS AND CALCULATIONS:

9.1 Clinical Score

Rats were examined for signs of arthritogenic responses in peripheral joints daily 3 times a week. Arthritis reactions were reported for each paw according to a 0-4 scale in ascending order of severity as shown below:

Arthritis Score	***Grade***
No reaction, normal	0
Mild, but definite redness and swelling of the ankle/wrist or apparent redness and swelling limited to individual digits, regardless of the number of affected digits	1
Moderate to severe redness and swelling of the ankle/wrist	2
Redness and swelling of the entire paw including digits	3
Maximally inflamed limb with involvement of multiple joints	4

The data were expressed as mean clinical score of all 4 paws.

9.2 Paw Volume evaluation:

The paw volumes of the hind paws were measured using a Plethysmometer. Then values were averaged.

9.3 Humane Endpoints:

At the end of the study, the animals were euthanized with Pentobarbitone Sodium (>100 mg/kg IP).

10. ANIMAL CARE AND USE STATEMENT:

This study was performed following an application-form reviewed by the Committee for Ethical Conduct in the Care and Use of Laboratory Animals, and pending their approval that the study complied with the rules and regulations set forth.

11. RESULTS:

11.1 Clinical signs:

No abnormalities were detected in any of the treated groups.

11.2 Body Weights (Table 1, Figure 1)

Vehicle treated animals gained 15% of body weight and TI treated animals gained about 21% of body weight during 28 days, the entire study period. Group 4F, Dexamethasone treated animals gained only 2% body weight - this phenomenon was common.

11.3 Arthritogenic Responses (Table 2, Figure 2)

Until study day 12 no disease signs were noticed in any of the animals participated in the study. On study day 12, 3 out of 10 animals of the vehicle were ill, expressing disease in several joints. The disease severity increased and the number of incidences increased during the remaining study period. On study day 28, 7 out of 10 of the vehicle treated animals showed a significant disease expressed as multi joints welling and inflammation in more that one paw (Average Clinical Score of 1.5±0.4 points. Dexamethasone, the positive control in this study, at a dose of 1 mg/kg administered IP starting on day of study commencement prevented disease development completely (Mean Clinical Score on day 28: Vehicle treated group (1F): 1.5±0.4; Dexamethasone treated group (4F): 0.0±0.0; $p<0.01$ vs. vehicle treated group).

GB-67B administered at a dose of 30 mg/kg PO starting on study day 0 (groups 3F) was slightly active in reducing disease signs. Clinical Score on study day 28 for 3F group of GB-67B was 0.9±0.4 $p<0.05$).

11.4 Paw Volume (Table 3, Figure 3)

Mean animal paw volume as measured by the Plethysmometer increased during the 28 days of the study by 77±11% in the vehicle treated animals (Group 1F). Dexamethasone treatment (Group 4F) completely prevented this increase in paw volume. On study day 28 the mean paw volume of the Dexamethasone treated animals was only 0.2±0.7% higher than baseline. GB-67B reduced paw volume in a dose related manner, whereas the highest dose tested in this study reduced paw volume by 50%.

12. CONCLUSIONS:

In view of the findings obtained under the conditions of this study and confined to the in-life data, GB-67B was active in reducing the arthritic clinical score and paw volume in the AIA model for arthritis.

13. TABLES AND FIGURES:

Table 1: Mean Group Body Weight (g):

Treatment	Study Days	0	3	6	9	12	15	18	21	24	28
Vehicle (Group 1F)	Mean	133	134	137	142	147	147	148	149	150	153
	SEM	4	3	3	3	3	3	3	4	4	4
GB-67B 10 mg/kg (Group 2F)	Mean	130	126	131	140	148	148	149	152	153	157
	SEM	3	5	5	3	4	4	3	3	3	3
GB-67B 30 mg/kg (Group 3F)	Mean	133	123	128	141	147	149	151	155	159	161
	SEM	3	4	4	2	2	2	3	3	2	2
Dexamethasone (Group 4F)	Mean	132	127	127	128	129	127	126	129	132	135
	SEM	2	2	2	3	2	2	2	2	2	3

Figure 1: Mean Group Body Weight (g):

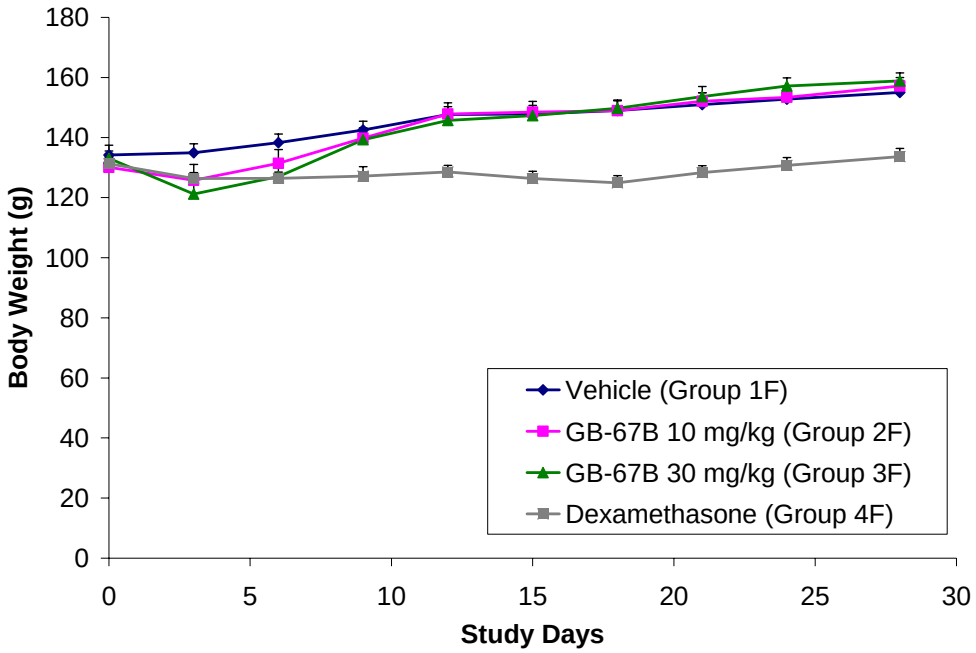


Table 2: **Mean Group Arthritis Score**:

- P<0.05 vs. vehicle
-

Treatment	Study Days	0	9	12	15	18	21	24	28
Vehicle (Group 1F)	Mean	0.0	0.0	0.6	1.1	1.4	1.5	1.6	1.5
	SEM	0.0	0.0	0.3	0.4	0.4	0.4	0.4	0.4
GB-67B 10 mg/kg (Group 2F)	Mean	0.0	0.0	0.2	0.7	0.9	1.1	1.1	1.1
	SEM	0.0	0.0	0.1	0.2	0.3	0.4	0.4	0.4
GB-67B 30 mg/kg (Group 3F)	Mean	0.0	0.0	0.1	0.4*	0.5*	0.7*	0.8	0.9
	SEM	0.0	0.0	0.0	0.3	0.3	0.3	0.3	0.4
Dexamethasone (Group 4F)	Mean	0.0	0.0	0.0	0.0*	0.1*	0.0*	0.0*	0.0*
	SEM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Figure 2: **Mean Group Arthritis Score**:

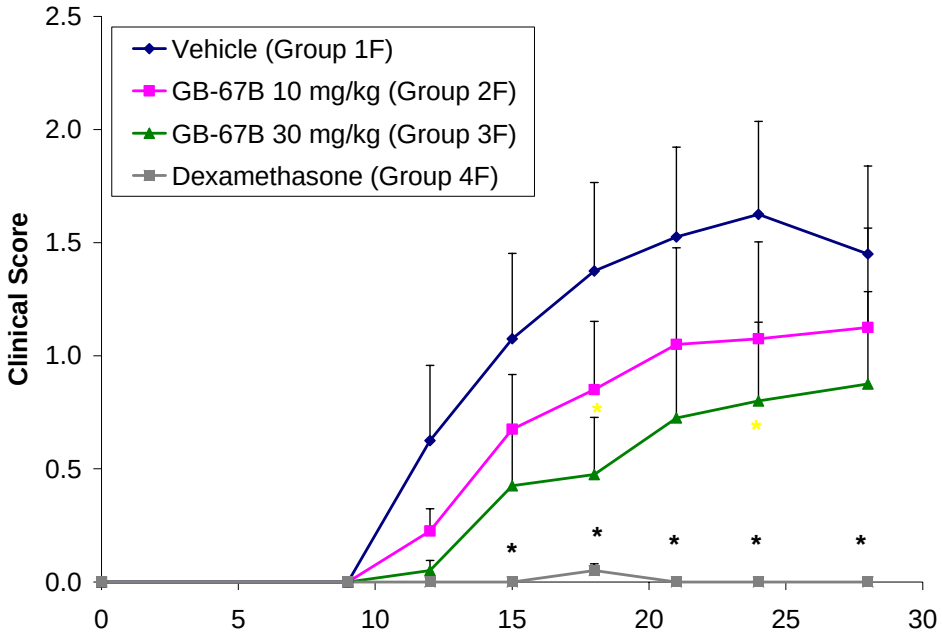


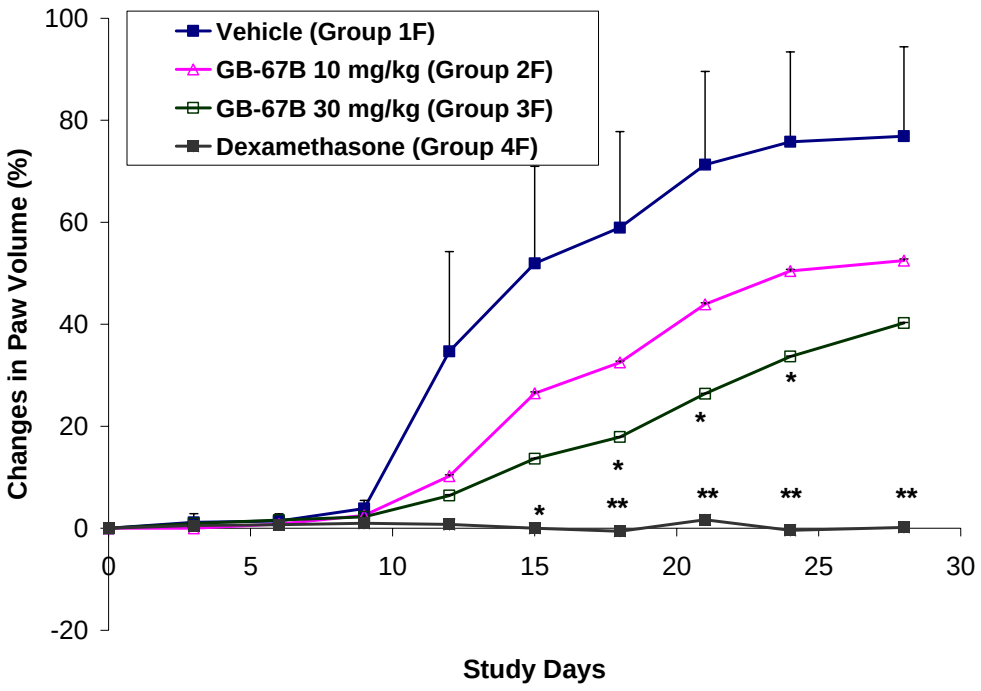
Table 3: Mean Group Changes in Paw Volume (%)

***p<0.05 vs. vehicle; **p<0.01 vs. Vehicle**

Treatment	Study Days	0	3	6	9	12	15	18	21	24	28
Vehicle (Group 1F)	Mean	0	1	1	4	35	52	59	71	76	77
	SEM	0.0	1.7	1.4	1.6	19.6	19.0	18.8	18.3	17.6	17.5
GB-67B 10 mg/kg (Group 2F)	Mean	0	0	1	3	10	26	33	44	50	52
	SEM	0.0	0.5	0.8	0.6	0.2	0.3	0.3	0.3	0.3	0.3
GB-67B 30 mg/kg (Group 3F)	Mean	0	1	2	2	6	14	18*	26*	34*	40
	SEM	0.0	0.9	0.9	0.4	0.2	0.1	0.1	0.1	0.1	0.1
Dexamethasone (Group 4F)	Mean	0	1	1	1	1	0*	-1**	2**	0**	0**
	SEM	0.0	0.8	0.7	0.2	0.1	0.0	0.0	0.0	0.0	0.0

Figure 3: Mean Group Changes in Paw Volume (%)

***p<0.05 vs. vehicle; **p<0.01 vs. vehicle**



14. INDIVIDUAL DATA

Body Weight (g)

DE- Animal was culled due to high arthiritis score (Ethical restrictions)

		Study Days									
Treatment & Group #	**Animal #**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**
Vehicle Group 1F	**1**	132	136	140	145	148	150	154	161	164	167
	2	137	139	142	148	153	150	152	141	142	140
	3	127	131	139	143	150	153	156	152	155	159
	4	122	124	130	133	135	DE	DE	DE	DE	DE
	5	132	135	138	145	154	152	150	143	143	145
	6	123	137	140	146	147	145	147	142	142	149
	7	114	123	125	129	137	135	137	132	133	135
	8	153	115	117	121	130	132	133	147	143	150
	9	148	150	152	154	158	163	167	173	178	177
	10	142	149	151	154	158	156	155	DE	DE	DE
GB-67B 10 mg/kg Group 2F	**1**	130	105	115	133	144	148	153	156	157	162
	2	125	126	130	132	139	139	140	147	145	151
	3	144	147	150	152	157	160	160	167	169	171
	4	115	91	105	122	128	132	135	145	149	152
	5	122	119	124	132	139	139	140	140	137	140
	6	132	111	119	136	146	148	150	159	159	163
	7	145	137	139	148	158	152	150	161	165	170
	8	127	129	131	136	139	141	139	146	145	150
	9	122	131	133	139	147	146	146	142	DE	DE
	10	155	154	160	166	176	178	177	165	160	163
	11	124	133	140	142	153	150	148	145	148	149
GB-67B 30 mg/kg Group 3F	**1**	140	140	141	144	147	147	151	157	159	161
	2	141	114	125	139	142	142	151	154	156	159
	3	120	125	130	135	143	141	142	146	149	152
	4	120	102	110	128	139	143	147	168	163	162
	5	135	125	131	147	152	155	159	162	168	170
	6	129	102	118	136	141	140	138	130	DE	DE
	7	137	139	144	153	158	159	160	159	154	154
	8	148	127	138	144	159	162	167	167	169	169
	9	138	141	140	143	148	149	148	153	160	162
	10	128	128	132	136	145	150	148	156	157	162
	11	129	104	115	127	129	132	136	138	136	137
Dexamethasone 1 mg/kg Group 4F	**1**	140	131	130	126	131	130	130	134	135	139
	2	139	134	135	153	133	134	133	134	138	137
	3	133	126	120	120	125	123	120	127	132	136
	4	130	125	127	124	130	127	123	130	134	135
	5	126	126	128	132	131	130	133	135	134	137
	6	123	120	121	124	122	120	117	117	118	120
	7	140	134	135	137	144	142	140	142	148	152
	8	139	134	135	134	132	131	130	132	136	140
	9	127	119	119	117	124	120	121	123	122	125
	10	120	118	118	114	118	114	112	118	122	126
	11	137	133	133	128	134	130	124	130	132	137

14.2 Arthritis Score

RL-Rear Left; RR- Rear Right; FL-Fore Left; FR-Fore right,

In red, last Clinical Score record before animal was culled due to the high Clinical Score (Ethical restrictions)

		Study Days															
		0				9				12				15			
Treatment & Group#	Animal #	RL	RR	FL	FR	RL	RR	FL	FR	RL	RR	FL	FR	RL	RR	FL	FR
Vehicle Group 1F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	1	2	1	1
	3	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0
	4	0	0	0	0	0	0	0	0	4	4	4	2	4	4	4	2
	5	0	0	0	0	0	0	0	0	1	1	0	1	2	1	1	1
	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	0	0	0	0	0	0	0	0	0	1	0	0	1	2	0	0
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10	0	0	0	0	0	0	0	0	2	3	1	1	4	4	3	2
GB-67B 10 mg/kg Group 2F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	1	1	1	1	3	2	1	2
	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0	2	0	0	1	2	3	1
	10	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	0
	11	0	0	0	0	0	0	0	0	1	1	0	0	2	4	0	1

GB-67B 30 mg/kg Group 3F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
	6	0	0	0	0	0	0	0	0	1	1	0	0	4	3	4	1
	7	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dexamethasone 1 mg/kg Group 4F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

		Study Days															
		18				21				24				28			
Treatment & Group#	**Animal #**	**RL**	**RR**	**FL**	**FR**	**RL**	**RR**	**FL**	**FR**	**RL**	**RR**	**FL**	**FR**	**RL**	**RR**	**FL**	**FR**
Vehicle Group 1F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	1	2	2	2	2	3	2	2	2	3	2	2	2	3	1	1
	3	1	2	0	0	1	2	0	0	1	2	0	0	1	2	0	0
	4	4	4	4	2	4	4	4	2	4	4	4	2	4	4	4	2
	5	3	2	1	1	3	3	1	1	4	4	2	1	3	3	0	1
	6	2	2	0	0	3	3	0	0	3	3	0	0	3	3	0	0
	7	1	2	1	1	2	3	1	0	1	4	1	1	0	4	1	1
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10	4	4	3	4	4	4	3	4	4	4	3	4	4	4	3	4
GB-67B 10 mg/kg Group 2F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	3	2	1	2	3	3	2	1	3	2	2	1	3	3	2	1
	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	2	2	3	3	4	4	4	4	4	4	4	4	4	4	4	4
	10	2	2	1	0	2	3	1	0	3	4	1	0	3	4	2	0
	11	3	4	0	2	3	4	1	3	4	4	0	3	4	4	0	3
GB-67B 30 mg/kg Group 3F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	1	0	0	0	1	1	0	0	1	0	0	0
	3	1	2	0	0	1	2	0	0	1	1	0	0	1	1	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	4	3	3	1	4	4	4	2	4	4	4	2	4	4	4	2
	7	1	0	0	0	1	1	0	1	1	1	0	1	2	1	0	1
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	11	1	2	1	0	2	3	2	1	2	3	2	3	3	4	3	4

Dexamethasone 1 mg/kg Group 4F	1	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	11	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

14.3 Paw Volume (ml):

DE- animal was culled due to high Clinical Score (Ethical restrictions)
RL-Rear Left; RR- Rear Right
In red, last measurement record before animal was culled due to high Clinical Score (Ethical restrictions)

		Study Days									
		0		3		6		9		12	
Treatment & Group#	Animal #	RL	RR	RL	RR	RL	RR	RL	RR	RL	RR
Vehicle Group 1F	1	1.4	1.6	1.5	1.6	1.5	1.5	1.6	1.6	1.6	1.7
	2	1.7	1.5	1.6	1.5	1.7	1.6	1.7	1.7	1.7	1.8
	3	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.8	1.8
	4	1.2	1.7	1.7	1.7	1.7	1.6	1.7	1.7	4.2	4.8
	5	1.6	1.7	1.6	1.7	1.6	1.7	1.7	1.7	2.9	1.7
	6	1.7	1.5	1.7	1.6	1.7	1.6	1.7	1.7	1.8	1.7
	7	1.6	1.6	1.6	1.6	1.6	1.7	1.6	1.6	1.7	1.6
	8	1.7	1.7	1.6	1.6	1.6	1.7	1.7	1.6	1.8	1.7
	9	1.7	1.7	1.7	1.7	1.7	1.6	1.7	1.7	1.7	1.6
	10	1.7	1.7	1.7	1.6	1.6	1.6	1.7	1.7	2.4	2.7
GB-67B 10 mg/kg Group 2F	1	1.7	1.7	1.7	1.7	1.6	1.7	1.7	1.6	1.7	1.6
	2	1.5	1.5	1.5	1.5	1.5	1.6	1.6	1.7	1.7	1.7
	3	1.6	1.7	1.6	1.7	1.6	1.7	1.6	1.7	1.7	1.6
	4	1.7	1.7	1.7	1.7	1.6	1.6	1.6	1.7	1.6	1.8
	5	1.7	1.7	1.7	1.7	1.7	1.7	1.8	1.7	2.2	2.2
	6	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.6
	7	1.6	1.5	1.6	1.5	1.6	1.6	1.7	1.6	1.7	1.6
	8	1.6	1.7	1.6	1.6	1.6	1.7	1.6	1.7	1.7	1.6
	9	1.5	1.6	1.5	1.6	1.6	1.6	1.7	1.7	2.0	2.0
	10	1.6	1.7	1.6	1.7	1.6	1.7	1.6	1.7	1.7	1.7
	11	1.7	1.7	1.7	1.7	1.7	1.7	1.8	1.7	2.0	2.5
GB-67B 30 mg/kg Group 3F	1	1.6	1.6	1.6	1.6	1.6	1.6	1.7	1.7	1.7	1.7
	2	1.7	1.6	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.7
	3	1.5	1.6	1.6	1.6	1.6	1.6	1.7	1.7	1.8	1.7
	4	1.7	1.6	1.7	1.7	1.6	1.6	1.7	1.7	2.3	1.9
	5	1.7	1.7	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.6
	6	1.6	1.7	1.7	1.7	1.6	1.7	1.7	1.7	1.8	1.7
	7	1.6	1.6	1.6	1.6	1.6	1.7	1.7	1.6	1.8	1.6
	8	1.7	1.7	1.7	1.6	1.6	1.7	1.7	1.7	1.7	1.7
	9	1.7	1.6	1.7	1.6	1.7	1.7	1.6	1.7	1.7	1.6
	10	1.7	1.7	1.7	1.7	1.7	1.7	1.6	1.6	1.7	1.7
	11	1.7	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.9	1.7
Dexamethasone 1 mg/kg Group 4F	1	1.7	1.7	1.6	1.7	1.7	1.7	1.6	1.7	1.7	1.7
	2	1.5	1.6	1.6	1.6	1.6	1.7	1.7	1.6	1.6	1.6
	3	1.8	1.8	1.7	1.8	1.7	1.7	1.7	1.7	1.7	1.7
	4	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.6
	5	1.6	1.6	1.6	1.7	1.6	1.7	1.7	1.7	1.7	1.7
	6	1.6	1.6	1.6	1.6	1.7	1.7	1.7	1.7	1.6	1.7
	7	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.6	1.7	1.7
	8	1.8	1.7	1.7	1.7	1.7	1.7	1.6	1.7	1.7	1.7
	9	1.7	1.6	1.7	1.6	1.7	1.7	1.7	1.7	1.7	1.7
	10	1.7	1.7	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.7
	11	1.7	1.7	1.7	1.7	1.7	1.7	1.6	1.7	1.6	1.7

		Study Days									
		15		18		21		24		28	
Treatment & Group#	**Animal #**	**RL**	**RR**	**RL**	**RR**	**RL**	**RR**	**RL**	**RR**	**RL**	**RR**
Vehicle Group 1F	1	1.6	1.7	1.8	1.7	1.8	1.8	2.1	1.9	1.9	2.1
	2	1.7	1.9	1.8	1.9	2.6	2.2	2.5	2.7	2.6	2.6
	3	1.8	1.8	1.9	2.0	1.9	2.3	2.0	2.4	2.3	2.0
	4	4.2	4.8	4.2	4.8	4.2	4.8	4.2	4.8	4.2	4.8
	5	2.5	2.5	2.7	2.6	2.9	2.8	3.1	3.0	3.0	3.2
	6	2.7	2.6	3.2	2.7	3.3	2.7	3.3	2.8	2.7	3.3
	7	1.7	2.4	1.9	2.7	3.2	3.1	3.0	3.1	3.1	3.1
	8	1.8	1.8	1.8	1.8	1.9	1.8	1.8	1.9	1.9	1.8
	9	1.6	1.8	1.7	1.9	1.8	2.0	1.9	2.1	2.2	1.9
	10	3.7	3.6	3.7	3.8	3.7	3.8	3.7	3.8	3.7	3.8
GB-67B 10 mg/kg Group 2F	1	1.7	1.7	1.7	1.7	1.8	1.7	1.8	1.8	1.8	1.9
	2	1.7	1.7	1.8	1.7	1.7	1.8	1.8	1.8	1.8	1.8
	3	1.8	1.8	1.8	1.8	1.8	1.8	1.9	1.8	1.9	2.0
	4	1.7	1.7	1.7	1.8	1.8	1.8	1.8	1.9	1.9	1.8
	5	2.7	3.0	3.5	2.7	3.2	3.1	3.1	3.1	3.1	3.1
	6	1.9	1.7	1.7	1.8	1.8	1.8	1.8	1.9	1.9	1.9
	7	1.8	1.8	1.9	1.8	1.8	1.8	1.9	1.8	1.9	1.9
	8	1.7	1.7	1.8	1.8	1.8	1.8	1.8	1.8	1.9	1.8
	9	1.8	2.2	2.6	2.5	3.0	3.9	3.0	3.9	3.0	3.9
	10	2.0	2.0	2.1	2.2	3.0	2.9	3.3	3.6	3.7	3.3
	11	2.9	4.6	2.7	4.8	3.1	4.5	3.9	4.7	4.7	4.0
GB-67B 30 mg/kg Group 3F	1	1.7	1.8	1.7	1.8	1.8	1.8	1.8	1.8	1.9	1.8
	2	1.7	1.6	1.7	1.7	1.8	1.7	1.9	1.7	1.8	1.9
	3	1.7	1.8	1.8	1.7	2.2	2.2	2.1	2.2	2.1	2.2
	4	1.7	1.8	1.7	1.8	1.8	1.8	1.8	1.9	1.9	1.9
	5	1.8	1.7	1.8	1.8	1.8	1.8	1.8	1.9	1.8	1.8
	6	3.9	2.5	4.0	2.9	4.6	3.2	4.6	3.2	4.6	3.2
	7	1.8	1.7	1.8	1.7	1.8	1.8	2.3	2.7	2.7	2.3
	8	1.8	1.8	1.8	1.9	1.8	1.9	1.9	1.8	1.9	1.9
	9	1.7	1.7	1.7	1.7	1.8	1.7	1.8	1.8	1.8	1.8
	10	1.6	1.8	1.7	1.7	1.8	1.8	1.8	1.8	2.7	3.0
	11	1.6	1.8	1.7	2.2	2.2	2.5	2.8	2.6	2.8	2.6
Dexamethasone 1 mg/kg Group 4F	1	1.7	1.7	1.6	1.7	1.5	1.6	1.6	1.6	1.6	1.6
	2	1.6	1.6	1.7	1.6	1.7	1.6	1.7	1.6	1.6	1.7
	3	1.6	1.7	1.6	1.7	1.7	1.7	1.6	1.7	1.7	1.7
	4	1.7	1.6	1.6	1.6	1.7	1.7	1.6	1.6	1.6	1.6
	5	1.7	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.6
	6	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.6
	7	1.6	1.8	1.6	1.6	1.7	1.7	1.7	1.7	1.7	1.6
	8	1.7	1.6	1.7	1.7	1.8	1.7	1.7	1.7	1.7	1.7
	9	1.6	1.7	1.6	1.7	1.7	1.7	1.6	1.6	1.7	1.7
	10	1.6	1.7	1.6	1.6	1.6	1.6	1.6	1.6	1.7	1.6
	11	1.6	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7

15. APPROVAL SIGNATURES

Study Directors:

_____ _____
Sigal Meilin, PhD Date

Sponsor:

_____ _____
Gregory Bluemling Date