



# Glatiramer Acetate Depot: Towards Clinical Application

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- Background:
  - Glatiramer Acetate (GA) and GA Depot
  - GA Depot Formulation
- Objective
- Methods
  - In Vitro Release Profile of GA from GA Depot
  - Animal Studies
  - Questionnaire Study
- Results
  - In Vitro Release Profile of GA from GA Depot
  - Animal Studies
  - Questionnaire study
- Conclusions

- 34% (136,000) of the 400,000 patients diagnosed with Multiple Sclerosis (MS) in the US, are treated with glatiramer acetate (GA, marketed as Copaxone<sup>®</sup> <sup>1</sup>) as first line treatment
- GA (Copaxone<sup>®</sup>) has been used for ~20 years with good efficacy as well as excellent safety and tolerability profiles
- Daily GA adherence today is estimated at 70%<sup>2</sup> (for patients treated at least 6 months). This low adherence is correlated with increased relapse rate<sup>3</sup>, more ER visits and increased health related costs
- Main adverse events of GA include injection site reactions<sup>4</sup>
- Change of GA (Copaxone<sup>®</sup>) daily to thrice-weekly reduced the annualized rate of moderate-to-severe injection-related adverse events by 60%<sup>4</sup>

1. Margolis JM et al., "Disease-modifying drug initiation patterns in commercially insured multiple sclerosis patients: a retrospective cohort study", *BMC Neurology* 2011
2. Kleinman NL et al., "Medication adherence with disease modifying treatments for multiple sclerosis among US employees", *Journal of Medical Economics*, 2010
3. MerriKay Oleen-Burkey et al., "The relationship between alternative medication possession ratio thresholds and outcomes evidence from the use of Glatiramer Acetate", *Journal of Medical Economics*, 2011
4. Copaxone<sup>®</sup> prescribing information, FDA

- Glatiramer acetate (GA) long-acting injection
- Formulation based on GA-loaded PLGA microspheres, ~10 microns in size; releases 90% of GA within 30 days
- Microspheres are made of Poly (lactide-co-glycolide) (PLGA), a biodegradable polyester, used in FDA-approved drugs: Lupron<sup>®</sup>, Risperdal<sup>®</sup> Consta<sup>®</sup> and Vivitrol<sup>®</sup>
- Microspheres encapsulate the GA; there is no chemical connection to GA
- This is a different technology from Pegilation



- GA (Copaxone®) has been used for over 20 years with good efficacy and excellent safety and tolerability profile
- GA Depot aims to overcome Copaxone®'s frequent administration drawback which is mainly an adherence issue<sup>1</sup>, a fact that is correlated with an increased relapse rate<sup>2</sup>, more ER visits and increased health related costs
- GA Depot is aimed to reduce the number of injection site reactions, a limiting factor associated with administration of Copaxone®

**GA Depot will reduce treatment burden, which will increase patient adherence, resulting in decreased complications**

1. Kleinman NL et al., "Medication adherence with disease modifying treatments for multiple sclerosis among US employees", *Journal of Medical Economics*, 2010
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- To compare activity of GA Depot to Copaxone® in Experimental Autoimmune Encephalomyelitis (EAE) models in mice
- To assess the unmet need for such formulation among current Copaxone® patients
- To assess the GA Depot formulation's ability to fulfill Copaxone ® patients' unmet needs

- GA Depot is weighed and placed in a stirred vessel containing PBS at 37°C
- At designated time points, samples are retrieved and kept for analysis
- Concentration of GA in samples is determined using gel-permeation chromatography
- % release of GA from GA Depot is calculated

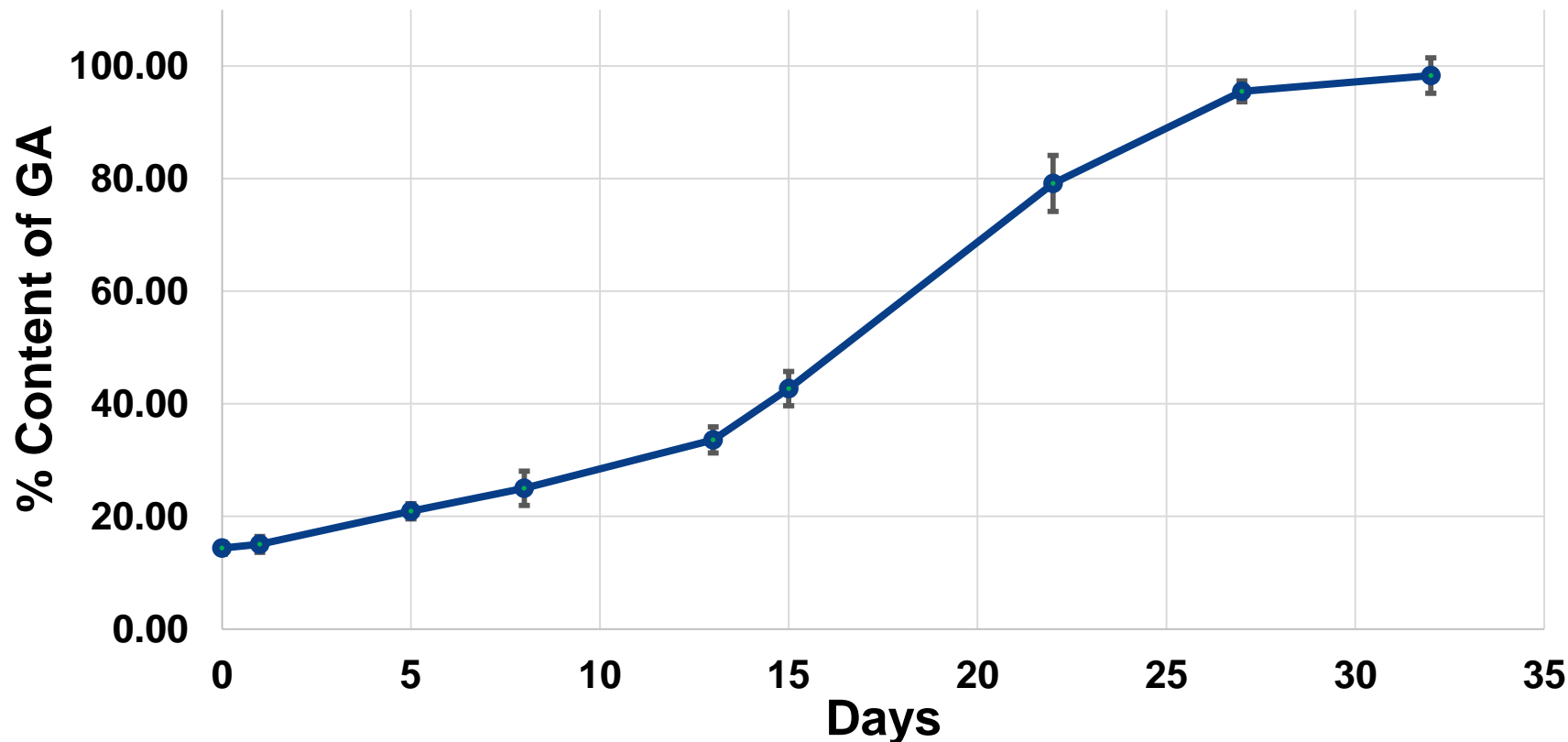
## Experimental Autoimmune Encephalomyelitis (EAE):

- CD4+ T cell-mediated autoimmune disease, characterized by primary demyelination of axonal tracks in the central nervous system (CNS), leading to progressive hind-limb paralysis
- Provides a powerful model for the study of CD4+ TH1/TH17-mediated tissue damage, generally considered to be a relevant model for MS
- **Animals:** C57BL/6 female mice, 7-9 weeks old
- **Induction of EAE:** emulsion of MOG 35-55 in modified Complete Freund's Adjuvant (CFA) was injected subcutaneously (SC) on the shaved back of the mouse at one site, followed by an intraperitoneal injection of Bordetella pertussis toxin in PBS on Day 0, and 48 hours post MOG immunization
- **Measurements:** Body weight was measured daily from Day 0 through Day 28. EAE was assessed by clinical scoring of the mice once-daily from Day 0 through Day 28 post-immunization



Score	Clinical Signs
0	Normal mouse; no overt signs of disease
1	Limp tail
2	Hind limb paralysis
3	Hind limb and front limb paralysis
4	Complete paralysis; sacrifice for humane reasons
5	Moribund state; death by EAE

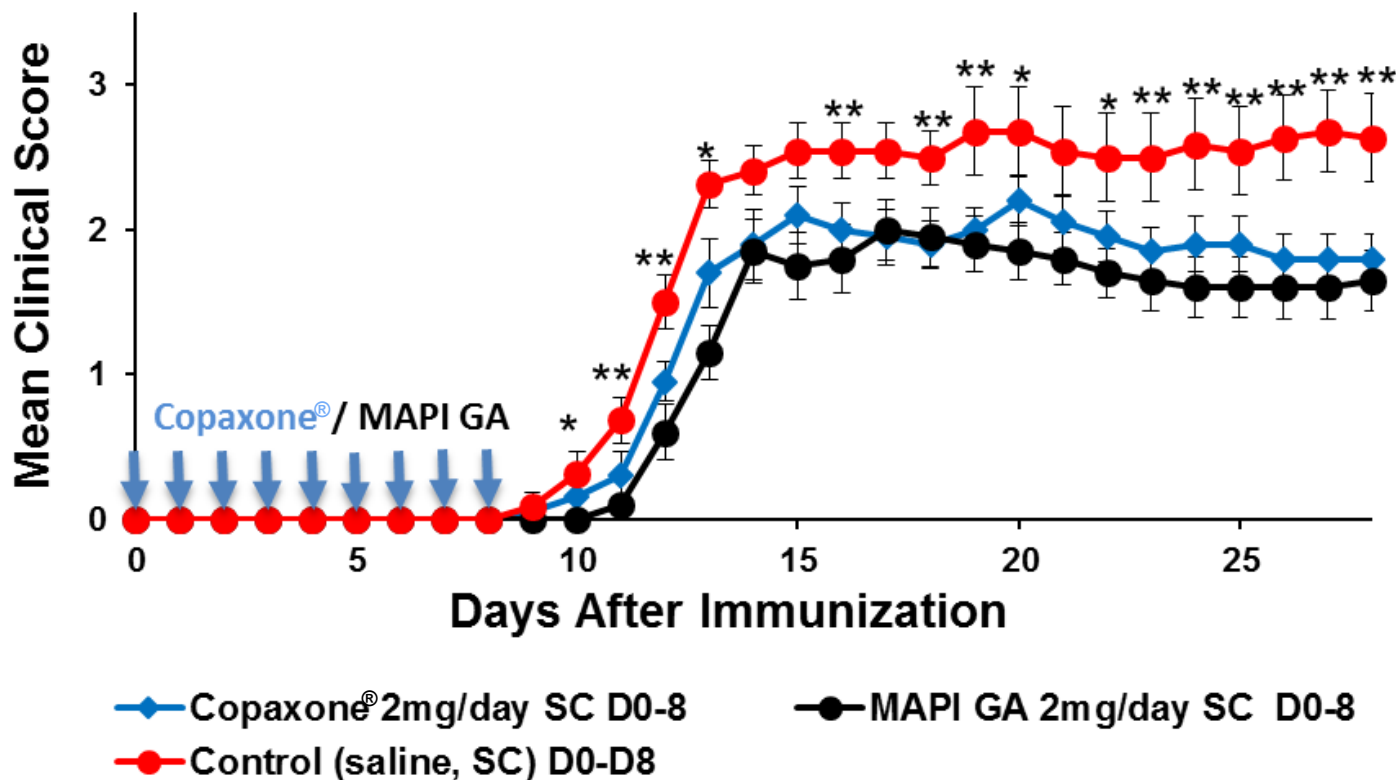
- Questionnaires include 43 questions covering:
  - General demographics
  - General quality of life
  - History of medication
  - Compliance to Copaxone<sup>®</sup> treatment
  - The effect of dosing regimen on quality of life
  - Local adverse events
  - Medical History
- Study population: Copaxone<sup>®</sup>-treated RRMS patients (at least 1 year); Can sign informed consent; Ages: 25-60
- The study aim was to assess the need for once-monthly treatment among daily Copaxone<sup>®</sup> users
- Study approved by Carmel MC IRB



**GA is steadily released from GA Depot during one month**

*Triplicate, batch no. P.GA.11081401, results presented +/- standard deviation*

## Mean Clinical Score



\*  $P < 0.05$  for MAPI GA compared with untreated control.

\*\*  $P < 0.05$  for all groups compared with untreated control, single factor ANOVA followed by one-tail two-sample  $T$  test assuming unequal variances,  $n = 10$  / group,  $\pm$  standard error.

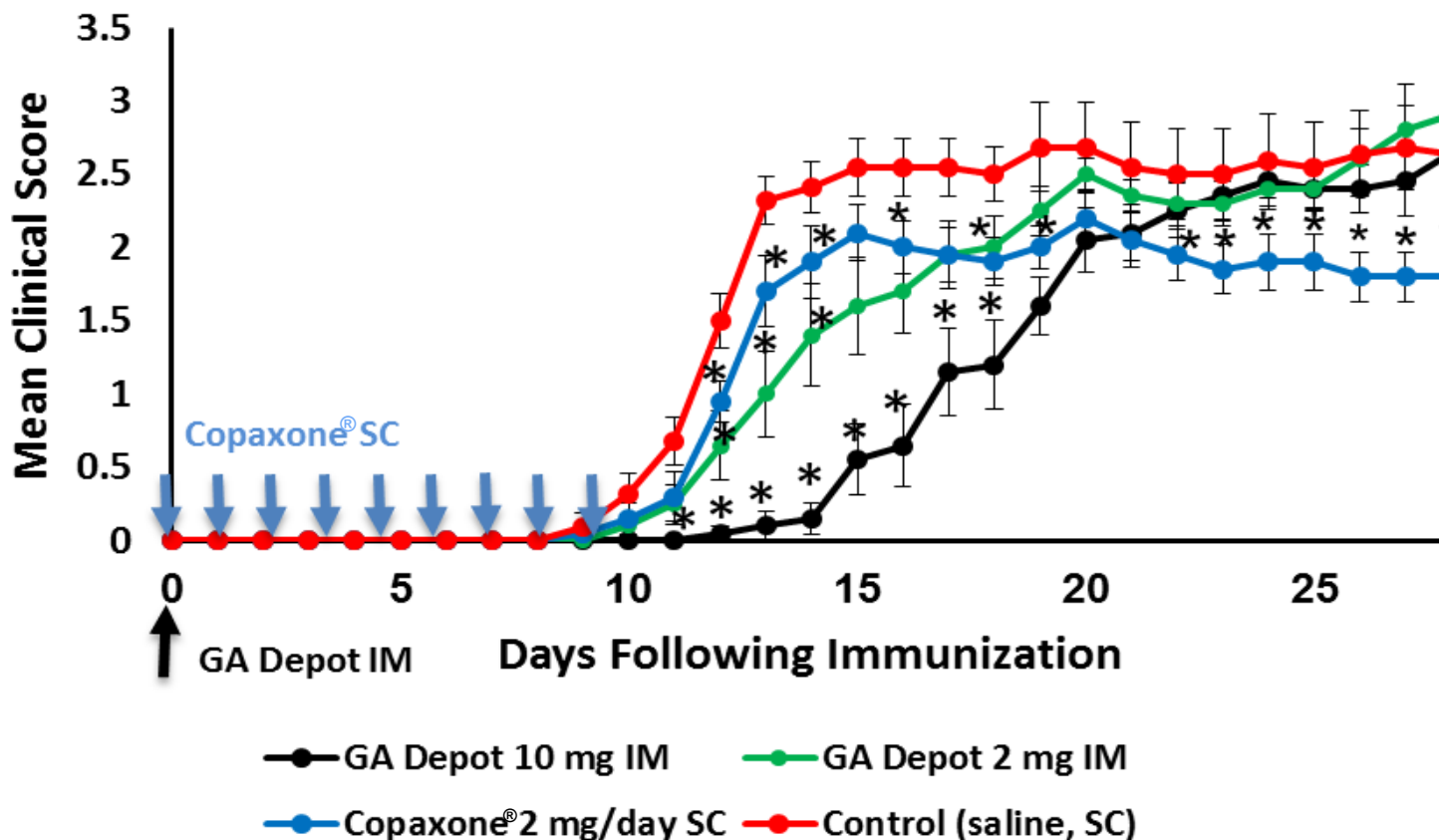
Groups	Maximum Mean Disease Score	Mean Disease Duration (days)	Mean Day of Onset	AUC Clinical Score (% from control)	Survival Rate at Day 28
GA Depot 10 mg (IM) D0,1	2.85±0.25	12.60±0.74*	16.40±1.67*	52.74±5.26*	90%
Copaxone® (SC) 2 mg/day, D0-D8	2.45±0.17*	17.30±0.49	11.70±0.49	74.41±5.15*	100%
MAPI GA (SC) 2 mg/day, D0-D8	2.15±0.66*	16.50±0.54*	12.50±0.54*	64.84±7.40*	100%
GA Depot 2 mg (IM) D0	3.05±0.33	16.20±0.71*	12.80±0.71*	80.70±5.55*	80%
Control (saline, SC), D0-D8	3.15±0.22	18.09±0.35	10.90±0.35	100.00±8.61	90%

n=10 / group, +/- standard error. \* P<0.05 compared with untreated control, single factor ANOVA followed by one-tail two-sample T test assuming unequal variances



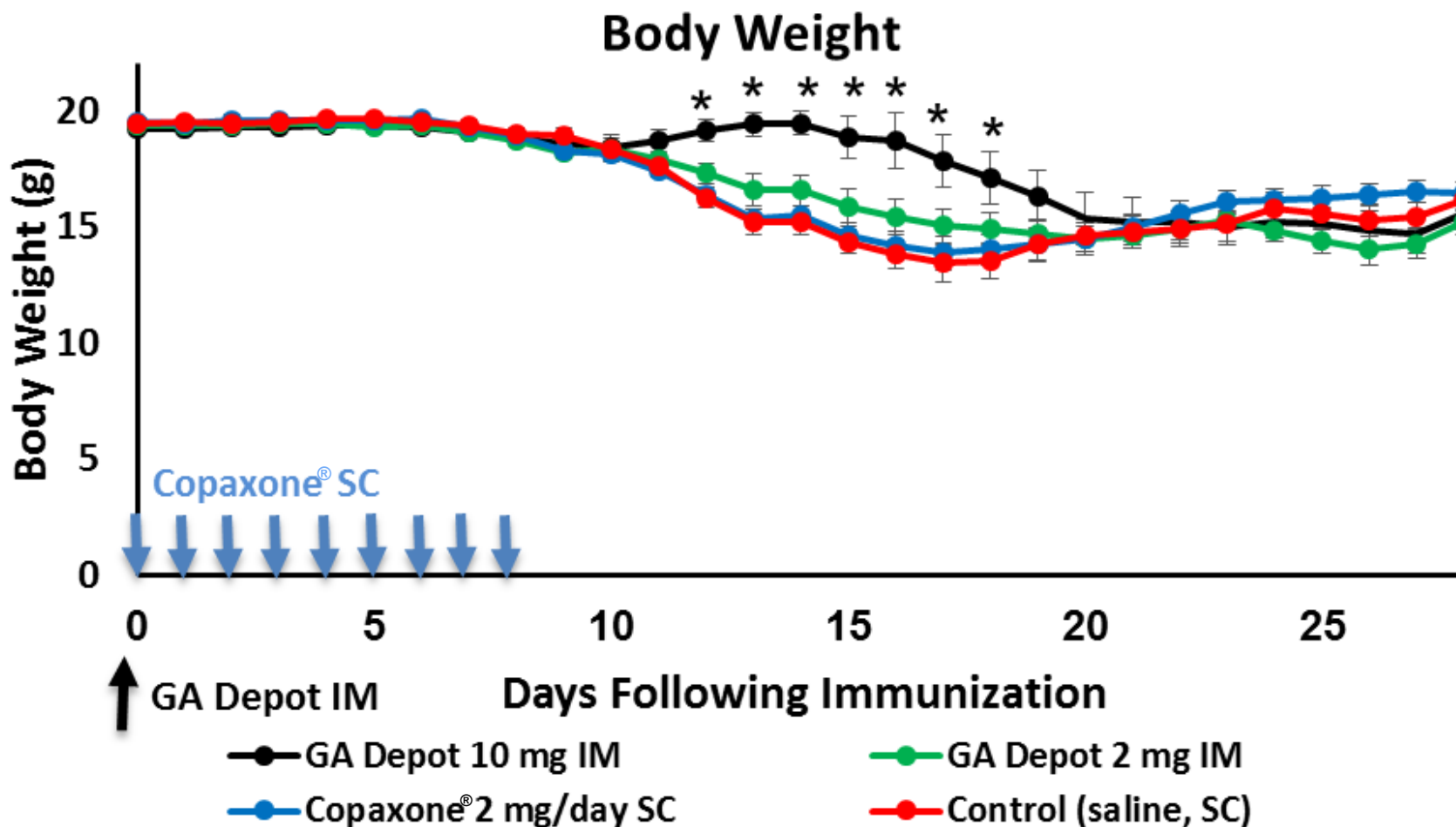
# Results: GA Depot Activity POC

## Mean Clinical Score



$n=10$  / group,  $\pm$  standard error

\* $P<0.05$  compared with untreated control, single factor ANOVA followed by one-tail two-sample  $T$  test assuming unequal variances



n=10 / group, +/- standard error. \*  $P < 0.05$  compared with untreated control, single factor ANOVA followed by one-tail two-sample T test assuming unequal variances

# Results: GA Depot Dose Response

Groups	Maximum Mean Disease Score	Mean Disease Duration (days)	Mean Day of Onset	AUC Clinical Score (% from control)	Survival Rate
GA Depot 10 mg IM D0,1	2.30±0.16	16.40±0.28***	11.6±0.28***	77.88±4.13*	100%
GA Depot 2.5 mg IM D0	3.15± 0.42	14.50±1.44***	13.5±1.44***	93.12±12.12	70%
GA Depot 1 mg D0, 14	3.55±0.46	17.20±0.27***	10.80±0.27***	123.86±13.41	50%
Copaxone®(SC) 2 mg/day, D0-D14	4.10±0.44	16.20±0.18***	11.80±0.18***	138.03±14.04**	30%
Control (saline, SC) D0-D14	2.70±0.27	17.90±0.09	10.10±0.09	100.00±11.95	90%

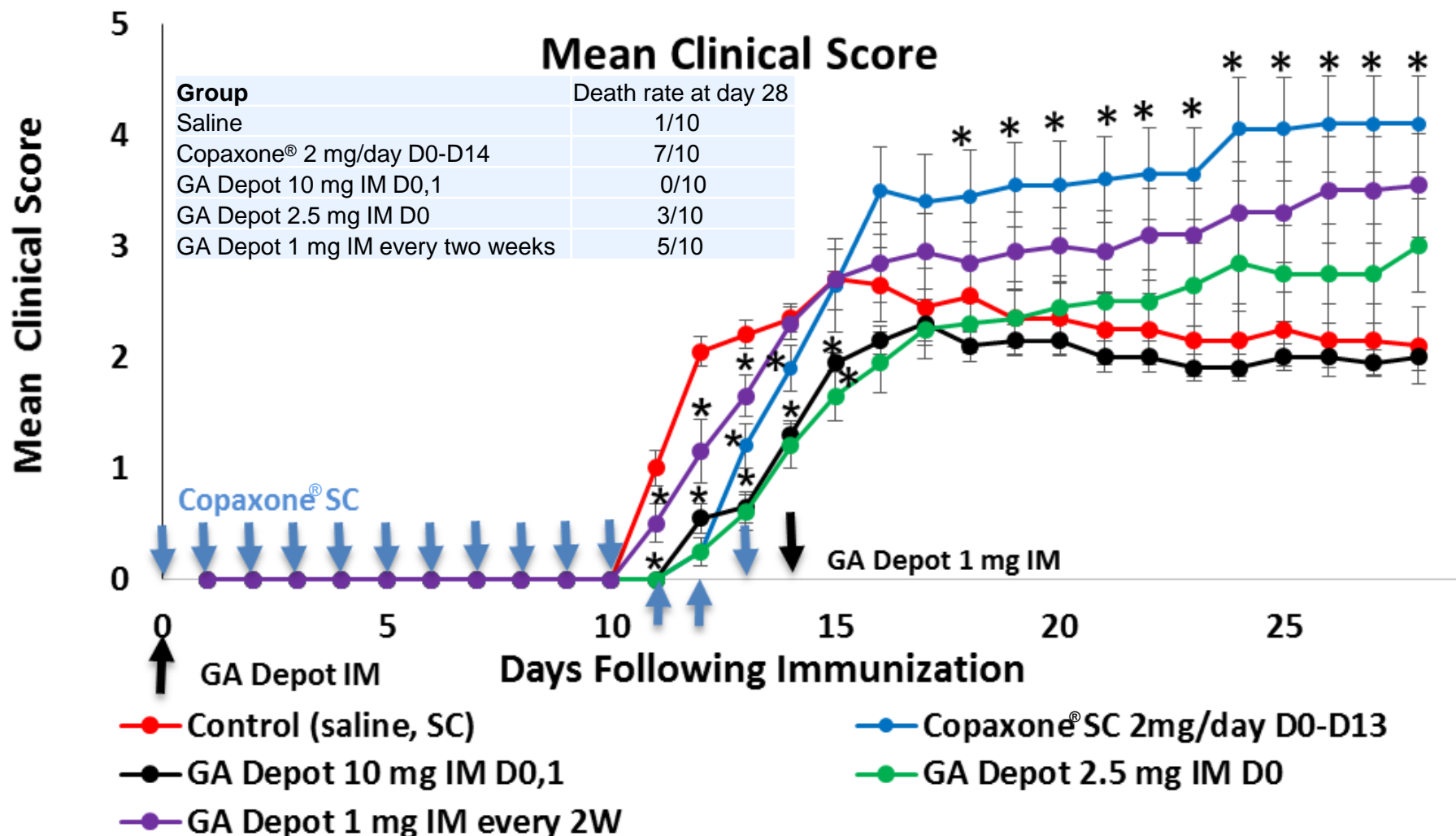
Data is presented ± standard error

\* P=0.054, \*\* P=0.027, \*\*\*P<0.05 compared with untreated control, Single Factor ANOVA followed by one-tailed T-Test assuming unequal variance





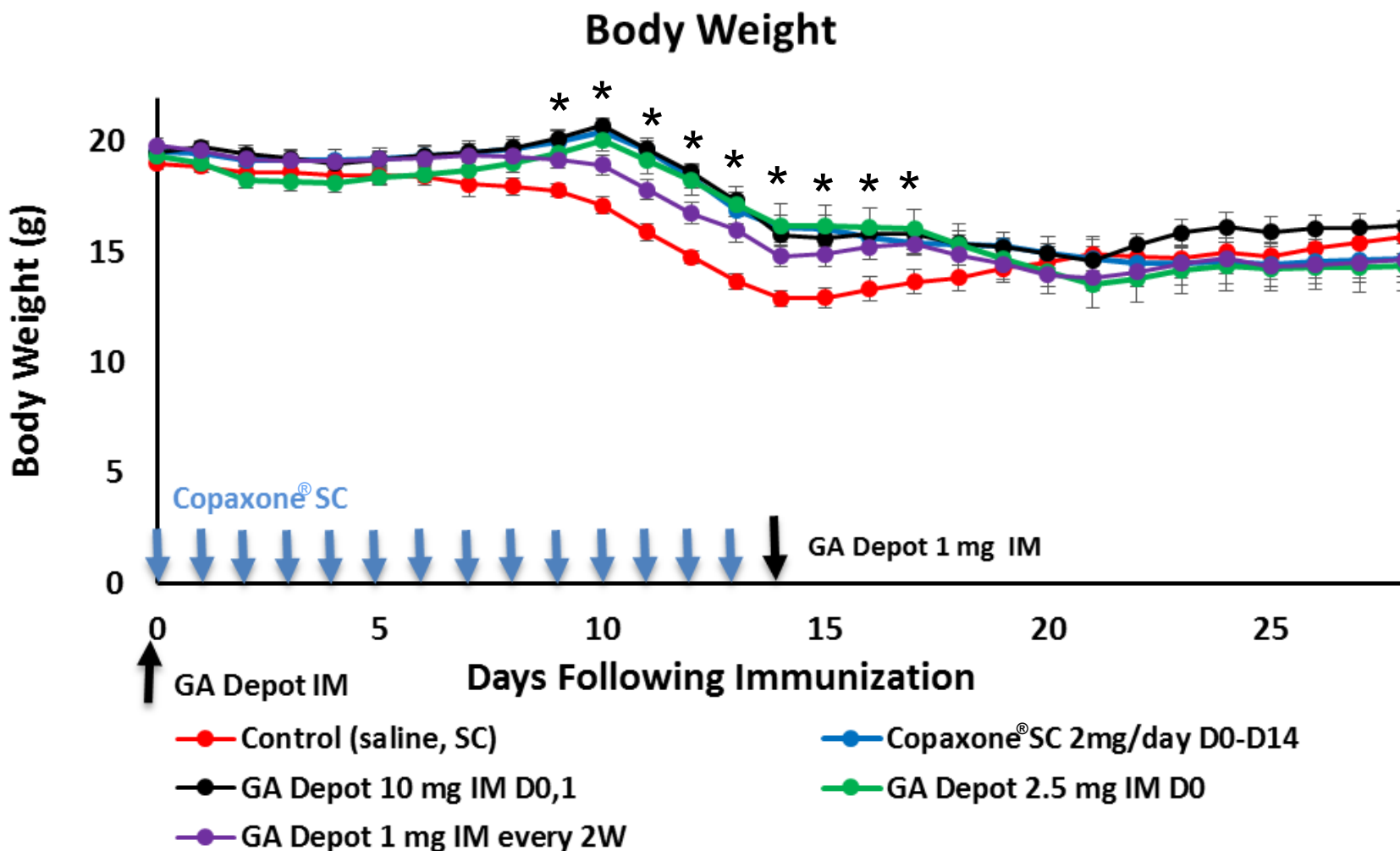
# Results: GA Depot Dose Response



n=10 / group, +/- standard error. \*P<0.05 compared with untreated control, Single Factor ANOVA followed by one-tailed T-Test assuming unequal variance



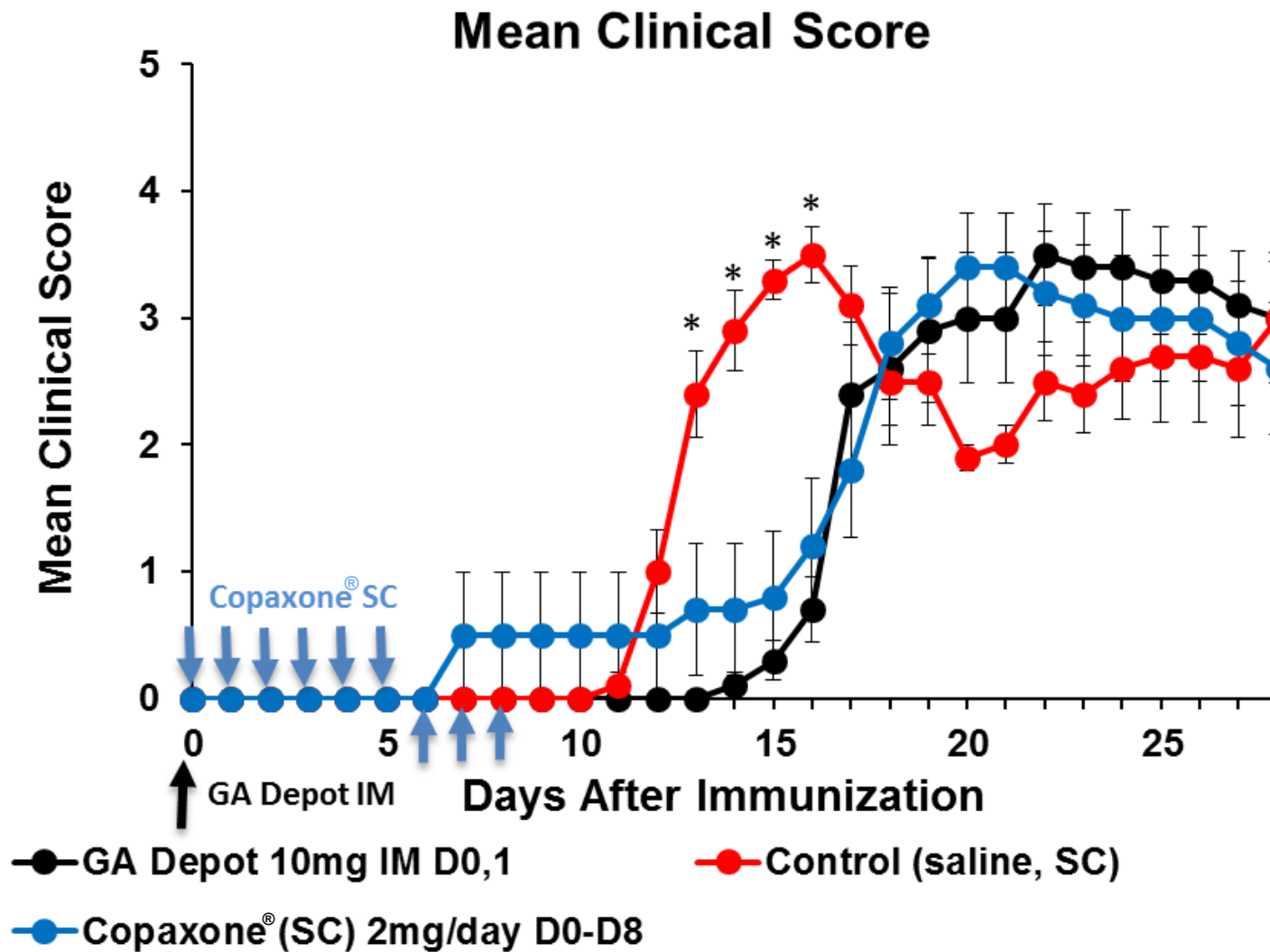
# Results: GA Depot Dose Response



n=10 / group, +/- standard error. \*P<0.05 compared with untreated control, Single Factor ANOVA followed by one-tailed T-Test assuming unequal variance



# Results: GA Depot Robustness

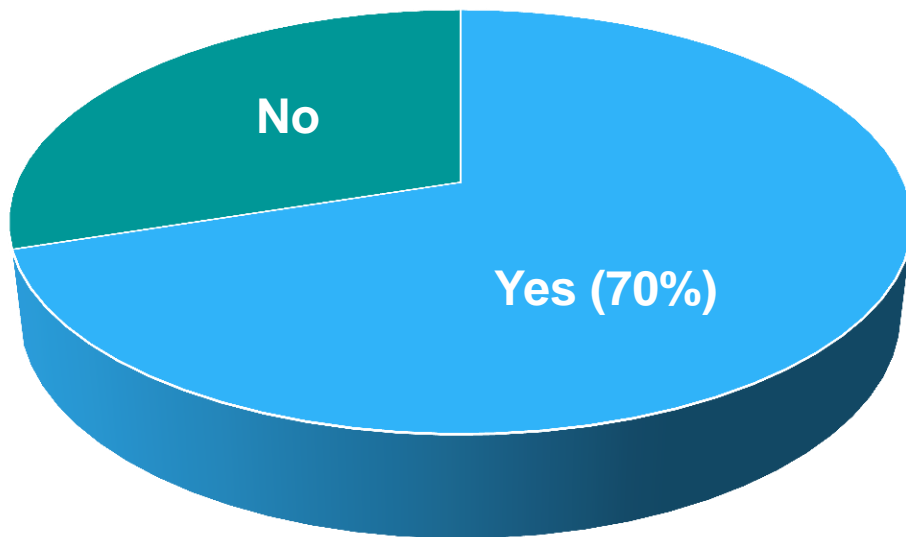


n=10 / group, +/- standard error. \*P<0.05 for all treatment groups compared with untreated control, Single Factor ANOVA followed by one-tailed T-Test assuming unequal variance

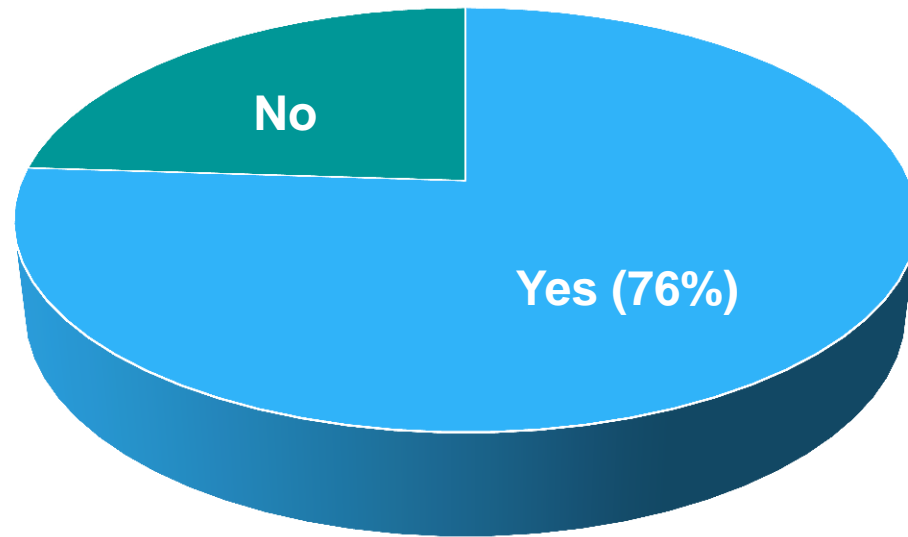
Question	Results		
Gender	Male	Female	
	23.8%	76.2%	
Age (years)	44.7 ± 9.9		
EDSS at study entry	3.1± 2.2		
Quality of life, in past year (1-10)	7.0 ± 2.3		
Had other treatment before Copaxone®	47.6%		
Reasons for change in treatment and switch to Copaxone®	AEs	Discomfort	Other
	60%	20%	20%
Full compliance to Copaxone® treatment	90.5%		
Satisfaction from Copaxone® (1-10)	9.2± 1.2		
Satisfaction from dose regimen of Copaxone (1-10)	6.6± 3.4		

Descriptive statistics, SAS® version 9.1

**Satisfaction from treatment will increase if frequency is reduced to once-monthly from once-daily**



**Willing to switch to GA Depot although it may cause increased injection site adverse events**



*Proportions of subjects that answered 5-10 (from a scale of 1-10) to above questions*

- In vitro, GA is gradually released from GA Depot over the course of 30 days
- In vivo:
  - MAPI's GA generates similar activity in MOG-EAE as treatment with Copaxone®
  - In all studies, GA Depot activity was at least as robust as Copaxone® in amelioration of EAE symptoms; results are reproducible
  - GA Depot demonstrates dose-response: 1 mg < 2.5 mg < 10 mg
- Questionnaires:
  - Patients' satisfaction from Copaxone® dosing regimen is lower than the satisfaction from the treatment itself
  - 70% of Copaxone® treated patients (for at least one year) declare that their satisfaction from treatment will increase if frequency of treatment will be reduced
  - 76% of Copaxone® treated patients (for at least one year) declare that they are willing to switch to GA Depot although it may cause increased injection site adverse events

- GA Depot can provide a steady supply of GA over the course of a month
- GA Depot can potentially be considered as a replacement for Copaxone® pending on clinical trials results
- There is an unmet need for a once-monthly formulation of GA
- Currently, a Phase II study is being conducted in Israel to test safety and tolerability of GA Depot
- Following successful pre-IND meeting with the FDA, in preparations towards single pivotal Phase III

- **Title:** a prospective 1-year, open-label, multicenter, Phase IIa study to assess safety, tolerability, and efficacy of once-a-month long-acting intramuscular injection of 80 mg glatiramer acetate (GA Depot) in subjects with RRMS
- **Number of Centers:** 4, in Israel
- **Investigational Product:** GA Depot 80 mg /4CC, IM , every four weeks

## Study Objectives to Evaluate:

- Primary: safety and tolerability
- Secondary: changes in MRI, EDSS and relapse rate from baseline

**Study Duration:** 1 year per patient; overall 5 quarters to results

**Population and Sample Size:** 20 subjects diagnosed with RRMS, treated with prior Copaxone<sup>®</sup> treatment for at least 12 months

**Status:** 11 patients recruited to date, sixth injections administered (5 patients)

- No relapses detected to date
- No related SAEs reported





# Thank you