# Clinical Study Protocol

A multinational, multicenter, randomized, Phase III, double blind, parallel group, placebo controlled study in subjects with Relapsing forms of Multiple Sclerosis (RMS) to assess the efficacy, safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered once every four weeks

Study Number Mapi GA Depot Phase III – 001

NCT04121221

Protocol with Amendment 03 approval date: 07 April 2021

**Mapi Pharma Ltd., Israel**
**CLINICAL TRIAL PROTOCOL**

| | |
|---|---|
| **Study Title:** | A multinational, multicenter, randomized, Phase III, double blind, parallel group, placebo controlled study in subjects with Relapsing forms of Multiple Sclerosis (RMS) to assess the efficacy, safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered once every four weeks |
| **Protocol No.:** | Mapi GA Depot Phase III – 001 |
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| **Protocol version/Date:** | 03 / 07 April 2021 |
| **Study Principal Investigator:** | [redacted] |
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| **Medical Director:** | [redacted] |
| **Name and title of persons authorized to sign the protocol for the Sponsor:** | [redacted] |

This clinical study will be conducted in accordance with Declaration of Helsinki and its updates, current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonization); US Code of Federal Regulations (Title 21, RFC Part 50. 56 and 312) and/or EU Directives; local country regulations and Sponsor's Standard Operating Procedures (SOPs).

| | | |
|---|---|---|
| **Name:** [redacted]<br>**Function:** [redacted]<br>Mapi Pharma Ltd. | [redacted] | [redacted] |
| | **Signature** | **Date** |
| **Name:** [redacted]<br>**Function:** [redacted]<br>Mapi Pharma Ltd. | [redacted] | 8.4.2021 |
| | **Signature** | **Date** |

**Confidentiality statement:**

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## Synopsis

| | |
|---|---|
| **Study title:** | A multinational, multicenter, randomized, Phase III, double blind, parallel group, placebo controlled study in subjects with Relapsing forms of Multiple Sclerosis (RMS) to assess the efficacy, safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered once every four weeks |
| **Sponsor:** | Mapi Pharma Ltd. |
| **Investigational product and formulation:** | [redacted] encapsulated glatiramer acetate for injection (GA Depot) suspended with sterile water for injection (WFI) |
| **Study phase:** | Phase III |
| **Indication:** | Treatment of relapsing forms of multiple sclerosis. |
| **Objectives:** | To assess the efficacy, safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered once every four weeks, as compared to placebo in a study design of 52 weeks' duration.<br>To assess the long-term safety and tolerability of GA Depot, in subjects treated for up to 104 weeks. |
| **Trial design:** | • Randomized<br>• Double blind placebo controlled<br>• Multinational |
| **Sample size and treatment:** | A total of [redacted] were originally planned to be randomized into this study to receive treatment with GA Depot or with matching placebo employing a 1:1 randomization [redacted]<br>Following the conduct of the pre-planned blinded, non-comparative, sample size reassessment the study size was increased to [redacted]<br>During the placebo controlled period (PC period, the first 52 weeks of the study immediately after randomization) subjects will receive either 40mg of GA Depot or matching placebo, IM, once every 4 weeks, [redacted].<br>Subjects who complete the PC period of the study will be offered to continue into the open label period (OL period) for an additional 52 weeks, in which all subjects will receive 40mg of GA Depot IM once every 4 weeks [redacted].<br>Subjects and sites will remain blinded to PC treatment assignment during both PC and OL Periods of the study. |
| **Clinical trial duration:** | Approximately 4 weeks of screening followed by a PC period of 52 weeks and subsequent OL period of an additional 52 weeks, followed by a 4-week follow-up period to assess subject's safety, for a total duration of up to 112 weeks. |

**Inclusion criteria:**

1. Adult subjects between 18-55 years of age, inclusive.
2. Subjects able to provide signed written informed consent.
3. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.
4. MS diagnosis fulfilling the 2017 McDonald Criteria.
5. Subjects should be ambulatory with an EDSS score of 0-5.5 at screening and baseline visits. EDSS score will be determined by a separate, blinded trained EDSS rater.
6. Subjects should be relapse free and neurologically stable from one month before screening visit and from screening visit to baseline visit.
7. No systemic corticosteroid treatment or ACTH within one month prior to screening visit.
8. Subjects must have experienced at least one of the following:
   i. At least one documented relapse in the 12 months prior to screening.
   ii. At least two documented relapses in the 24 months prior to screening.
   iii. One documented relapse between 12 and 24 months prior to screening, with at least one documented T1-Gd enhancing lesion in MRI performed within 0-12 months before screening.
9. Women capable of child bearing must have a negative urine pregnancy test at screening and baseline visit and use an adequate contraceptive[1] method throughout the study.

**Exclusion criteria:**

1. Use of experimental / investigational drug, and / or participation in drug clinical studies within the 6 months prior to screening.
2. Any off-label drug use for MS treatment such as high dose simvastatin and biotin within 6 months prior to screening.
3. Previous use of immunosuppressant including Mitoxantrone, Alemtuzumab, cladribine or any other cytotoxic agent within 5 years.
4. Previous use of natalizumab or any anti-B cell agent within 9 months prior to screening.
5. Previous use of Fingolimod or any other sphingosine-1-phosphate receptor modulator, Dimethyl Fumarate, Diroximel Fumarate (DRF), or Monomethyl fumarate within 2 months prior to screening. Subjects will be excluded if they do not have a lymphocyte count of above 1,000/$mm^3$ at screening.
6. Previous use of Teriflunomide within 12 months if no accelerated elimination procedure was used.
7. Previous treatment with immunomodulators (including IFNβ 1a and 1b, and IV Immunoglobulin (IVIg) within 2 months prior to screening.
8. Previous use of GA or any other glatiramoid.
9. Chronic (more than 30 consecutive days) systemic (IV, PO or IM) corticosteroid treatment within 6 months prior to screening visit.
10. Previous total body irradiation or total lymphoid irradiation.

[1] For the adequate contraceptive methods in this study, see Inclusion/exclusion criteria in the study protocol

11. Previous stem-cell treatment, autologous bone marrow transplantation or allogeneic bone marrow transplantation.
12. Subjects with a clinically significant or unstable medical, psychiatric, or surgical conditions that would preclude safe and complete study participation, as determined by medical history, physical exams, ECG and/or abnormal laboratory tests; and or subjects with an increased risk of serious Covid-19 related morbidity. Such conditions may include hepatic, renal or metabolic diseases, systemic disease, acute infection, current malignancy, or recent history (5 years) of malignancy, major psychiatric disorder, history of drug and/or alcohol abuse and allergies that could be detrimental according to the investigator's judgment.
13. Subjects who have >10 T1-Gd enhancing lesions at screening.
14. A known history of sensitivity to Gadolinium.
15. Inability to successfully undergo MRI scanning.
16. Pregnant or breast-feeding women.
17. Abnormal renal function (serum creatinine >1.5xULN or creatinine clearance <60 ml/min).
18. Abnormal liver function (transaminases >2xULN).
19. History of any anaphylactic reaction and/or serious allergic reaction following a vaccination, a proven hypersensitivity to any component of the study article (e.g., GA, Polyglactin, PVA).
20. Positive testing or a history of positive testing for syphilis, HIV, hepatitis, or tuberculosis.
21. Known or suspected history of drug or alcohol abuse.
22. Subjects diagnosed with any systemic autoimmune disease (other than MS) that may impact the CNS with MS like lesions such as Sarcoidosis, Sjögren's syndrome, Systemic Lupus Erythematosus (SLE), Lyme disease, Antiphospholipid antibodies (APLA) syndrome, etc. Subjects with stable local/organ autoimmune disease such as psoriasis, cutaneous lupus erythematosus, thyroiditis (Hashimoto's, Grave's) etc. may be considered eligible upon the investigator's discretion.
23. Any CNS disorder other than MS that may jeopardize the subject's participation in the study.
24. Subjects with uncontrolled diabetes.
25. Subjects with clotting disorders or receiving treatment with anticoagulants[2].

| | |
|---|---|
| **Dosage of investigational product:** | Subjects will be administered an IM injection of 40mg GA Depot [redacted] |
| **Comparator/control products:** | Placebo |
| **Modalities of drug administration:** | IM injection |

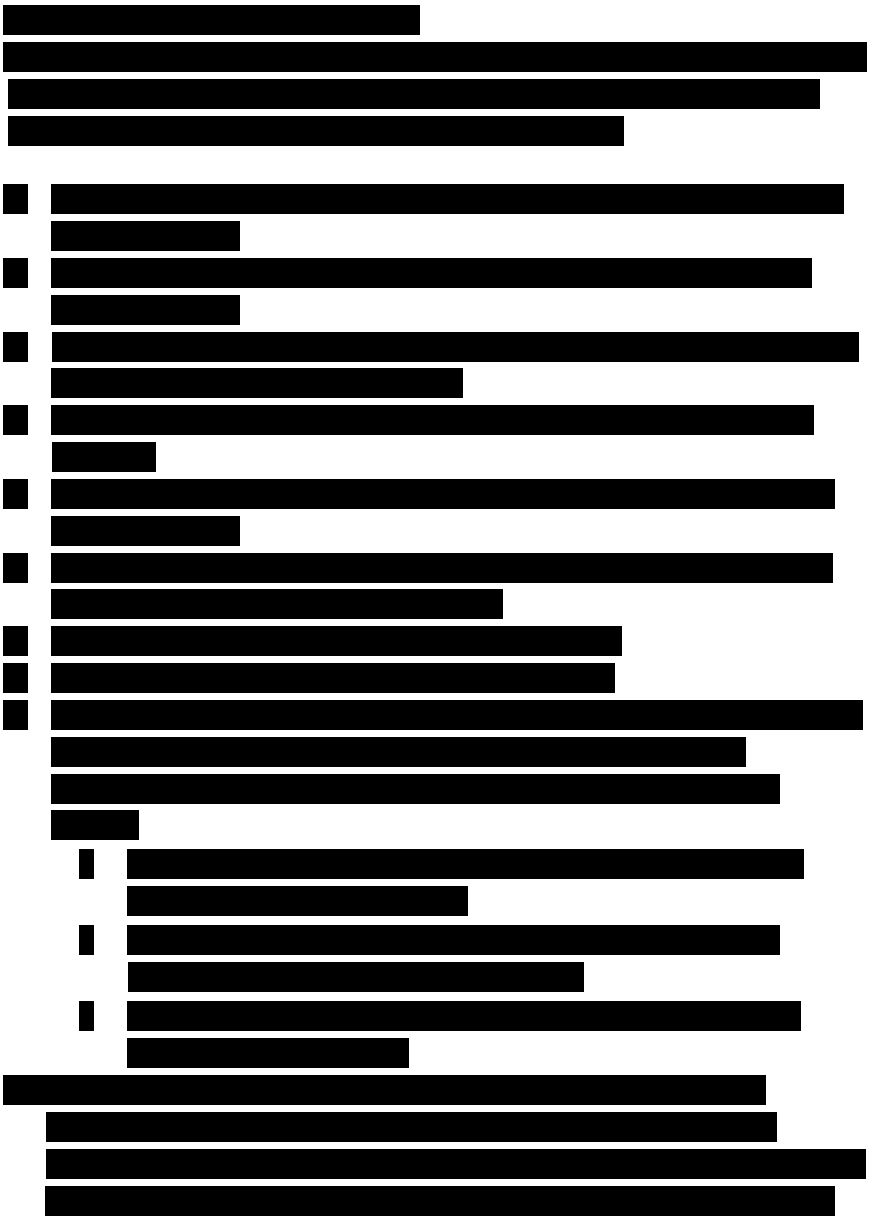
[2] The use of antiplatelet agents (such as Acetyl salicylic acid) is permitted during the study.

**Main study parameters:**

Primary Efficacy Endpoint:
Annualized Relapse Rate (ARR) during the 52 weeks of the PC period as derived from the total number of confirmed relapses.

Secondary Efficacy Endpoints:
All secondary endpoints will utilize the data collected only during the PC Period of the study.

1. Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline.
2. Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline.
3. Change from baseline to Week 52 in hyperintense T2-lesion volume.
4. Change from baseline to Week 52 in enhancing T1-lesion volume.



[redacted]

[redacted]

**Clinical trial procedures:**

The following are the study procedures:

During the PC period subjects will visit the site once every four weeks to receive GA Depot (40mg) or matching placebo as an IM injection administered by a health care professional (HCP). During the OL period all subjects will receive GA Depot.

Subjects will be evaluated [redacted]). During the OL period subjects will be evaluated [redacted].

[redacted]

A follow up (FU) visit to assess subjects' safety will be scheduled 4 weeks after the EoT visit, at week 108 for subjects continuing to the OL period, and at week 56 for those subjects electing not to continue to the OL period. A phone call will be scheduled within 4-

7 days following the first GA Depot or matching placebo injection, to check the subjects' well-being.

Following the screening evaluations, eligible subjects will be randomized to receive [redacted] of either GA Depot or matching placebo starting at visit 2 (baseline) and once every four weeks thereafter until week 52. The last visit of the PC period will be the baseline visit of the OL period. After week 52 (end of PC period), all subjects electing to continue into the OL period of the trial, will receive 13 administrations of GA Depot, for an additional treatment duration of 52 weeks until week 104, followed by a 4-week follow-up period until week 108 to assess subject's safety. Subjects and sites will remain blinded to PC treatment assignment during both PC and OL Periods of the study.

During the study, the following assessments are performed at designated time points:

- MRI scans will be conducted at screening, during the PC period at 24 and 52 weeks or at early termination visit [redacted] and at termination of the OL period at 104 weeks or at early termination visit [redacted] MRI will be performed at least 30 days after last treatment of steroids.
- Neurological evaluations will be performed [redacted]
- Follow-up safety assessment will be performed 4 weeks after study termination (EoT visit).
- MRI data will be conveyed to the central reading facility.
- Adverse events (AEs) will be monitored throughout the whole study period (PC and OL).
- Physical examination will be performed [redacted]
- Vital signs will be measured at all study visits during the PC and the OL periods.
- Phone call will be scheduled between 4-7 days following the first GA Depot or matching placebo injection to assess the subjects' well-being.
- Laboratory testing will be performed [redacted]:
  - [redacted].
  - Urinary pregnancy test in women of child-bearing potential at [redacted]
  - [redacted]

[redacted]

- ECG will be performed [redacted]
- Concomitant Medications will be monitored throughout the study.
- Patient-reported Quality of Life outcomes will be assessed [redacted]

Relapses will be monitored throughout the study. [redacted]

Re-consent Criteria:

In case of [redacted] following actions will be taken:

- The subject will be reminded of the currently available MS medications/treatments and the opportunity to terminate his/her participation in the study.
- The subject will be requested to re-sign an informed consent form if he/she chooses to continue to participate in the study, in the same treatment assignment.

An independent Clinical Trial Data Monitoring Committee (DMC) will be established according to the FDA's Guidance (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees; 2006). [redacted]

[3] [redacted]

The study drug will be administered and monitored on-site; [redacted]

Unscheduled visits may be performed as needed.

**Statistical Methodology:**

This multicenter, randomized, double blind, placebo-controlled study is designed to assess the efficacy, safety and tolerability of a long-acting IM injection of 40mg GA Depot administrated every four weeks as compared to placebo in subjects with RMS in a double-blind setting of 52 weeks. In addition, the study is designed to assess the long-term safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered every four weeks for a period of up to 104 weeks.

A total of [redacted] were originally planned to be randomized into this study to receive treatment with GA Depot or with matching placebo employing a 1:1 randomization scheme [redacted]. Following the conduct of the pre-planned blinded, non-comparative, sample size reassessment the study size was increased to [redacted].

The overall significance level for this study will be 5% using two-tailed tests. The gatekeeping approach will be used to maintain the overall type-I error due to multiple endpoints testing.

[redacted]

[redacted]

It is anticipated that some of the participating sites will recruit an insufficient number of subjects to allow estimation of within sites effect size or treatment by site interaction. Therefore, study centers will be pooled into geographical regions as will be detailed in the Statistical Analysis Plan (SAP) approved and signed before revealing of the randomization code.

**Overall Significance Level:**

The overall significance level for this study will be 5% using two-tailed tests. The study will have one primary endpoint and 4

secondary end-points ordered in a hierarchy and analyses will utilize the gatekeeping approach to maintain the experiment-wise type-I error of 5%. The order of the hierarchy of the secondary endpoints testing following the primary end-point testing is as follows:

1. Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline.
2. Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline.
3. Change from baseline to Week 52 in hyperintense T2-lesion volume.
4. Change from baseline to Week 52 in enhancing T1-lesion volume.

**Sample Size Rationale**:

[redacted]

**Principal Analysis of the Primary End-Point:**

The primary endpoint of the study is the Annualized Relapse Rate (ARR) during the 52 weeks of the PC period as derived from the total number of confirmed relapses [redacted]d.

Analysis of the primary endpoint will be based on the GA Depot vs. placebo contrast derived from the baseline adjusted over-dispersed,

exposure-weighted Poisson Regression (SAS® PROC GENMOD). [redacted]

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**Glossary and abbreviations**

| | |
|---|---|
| % | percent |
| °C | degree Celsius |
| AE | adverse event |
| ALT/SGPT | alanine aminotransferase |
| APLA | Antiphospholipid antibodies |
| AST/SGOT | aspartate aminotransferase |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| CBC | Complete blood cell count |
| CDMS | clinically definite multiple sclerosis |
| CDP | Confirmed disease progression |
| CNS | central nervous system |
| CPK | creatine phosphokinase |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| CTM | clinical trial material |
| DIT | dissemination in time |
| DMT | disease-modifying treatment |
| DMC | Independent Data Monitoring Committee |
| EAE | experimental autoimmune encephalomyelitis |
| ECG | electrocardiogram |
| EDSS | expanded disability status scale |
| EDTA | ethylene diamine tetraacetic acid |
| e.g. | *exempli gratia*, for example |
| eGFR | estimated glomerular filtration rate |
| EoT | End of treatment |
| [redacted]L | [redacted] |
| etc. | *et cetera*, and others |
| FDA | Food and Drug Administration |
| FS | Functional System |
| FU | Follow up |
| G | Gauge |
| GA | glatiramer acetate |
| GA Depot | glatiramer acetate long-acting injection |
| GCP | Good Clinical Practice |
| Gd | Gadolinium |
| GGT | gamma glutamyl transpeptidase |
| HCP | Health care professional |
| HR | heart rate |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonization |
| i.e. | *id est*, that is |
| IEC | independent ethics committee |
| IFN | Interferon |
| IgG | Immunoglobulin |
| IM | Intramuscular (ly) |
| IP | investigational product |
| IRB | institutional review board |

| | |
|---|---|
| ISRs | Injection site reactions |
| IV | Intravenous |
| IVMP | IV methylprednisolone |
| IVRS/IWRS | Interactive Voice/Web Response System |
| kg | Kilogram |
| L | Liter |
| LV | Lesion volume |
| LOCF | Last observation carried forward |
| MCH | mean corpuscular hemoglobin |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| min | minute(s) |
| mL | Milliliter |
| $mm^3$ | cubic millimeter |
| MOG | myelin oligodendrocyte glycoprotein |
| MPR | medication possession ratio |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| MSFC | multiple sclerosis functional composite |
| NEDA | No evidence of disease activity |
| NOAEL | no observed adverse effect level |
| OTC | over the counter |
| OL | Open label |
| *P* | Probability |
| *PC* | Placebo controlled |
| PBS | phosphate buffer saline |
| PBVC | Percent brain volume change |
| [redacted] | [redacted]d |
| PPMS | primary progressive multiple sclerosis |
| PR | PR duration in ECG |
| PVA | polyvinyl alcohol |
| QRS | QRS duration in ECG |
| QT | QT interval in ECG |
| QTc | QT interval corrected for heart rate |
| RBC | Red blood cell count |
| RR | RR interval in ECG |
| RRMS | relapsing remitting multiple sclerosis |
| RMS | relapsing forms of multiple sclerosis |
| RTSM | Randomization and Trial supply management |
| SAE | serious adverse event |
| T1 | spin-lattice relaxation time (time constant used with MRI) |
| [redacted] | [redacted] |
| U | unit |
| ULN | upper limit of normal |
| VDRL | Veneral Disease Research Laboratory |
| vs. | *versus*, as opposed to |
| WBC | White blood cell count |
| WFI | water for injection |

# 1 BACKGROUND INFORMATION

In addition to the information provided below, please also refer to the current GA Depot Investigator's Brochure and to the additional data provided by the Sponsor.

## 1.1 GA and GA Depot overview

Glatiramer acetate (GA) – also known as copolymer-1 and marketed world-wide under the trade name Copaxone® – is currently indicated for reduction of the frequency of relapses in subjects with relapsing forms of multiple sclerosis (RMS) by daily or three times a week subcutaneous injection.

RRMS (the major subtype of RMS) is the most common form of MS. It is defined as a chronic autoimmune disease of the central nervous system (CNS) in which subjects have relapses and periods of disease stability between relapses. Relapses are episodes of new or worsening neurological symptoms not caused by fever or infection that are constant and last more than 48 hours.

The mechanism by which GA exerts its effects in subjects with MS is not fully understood. However, GA is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in vitro systems suggest that upon its administration, GA-specific suppressor T-cells are induced and activated in the periphery.

Because GA can modify immune functions, concerns exist about its potential to alter naturally occurring immune responses. There is no evidence that GA does this, but this has not been systematically evaluated.

GA consists of the acetate salts of polypeptides containing L-glutamic acid, L-alanine, L-tyrosine and L-lysine, 4 amino acids that are found in myelin basic protein. The average molar fractions of the amino acids are 0.141, 0.427, 0.095, and 0.338, respectively and the average molecular weight of GA is 5,000 to 9,000 Daltons.

GA long-acting injection (GA Depot) is a combination of extended-release microspheres for injection and diluent for parenteral use. GA Depot is administered intramuscularly (IM).

[redacted]

The diluent for parenteral use is sterile water for injection. The microspheres are suspended in the diluent prior to injection.

Considerable data on the use of GA with subcutaneous administration in humans is available. Data on GA Depot from phase IIa in Israel is available in this protocol (see section 1.8).

## 1.2 Rationale for the use of GA Depot in subjects with RMS

GA is considered one of the first-line treatments for RMS and is widely used (1). Currently, GA treatment consists of daily or three times a week SC self-injection. The frequently observed injection-site adverse effects include irritation, hypersensitivity, inflammation and pain. Side effects generally include (beside the injection site reactions), aches, fever and chills, that are generally mild in nature. Over time, a visible dent at the injection site due to the local destruction of fat tissue, known as lipoatrophy, may develop (2). Therefore, an alternative method of administration is desirable. One of the main challenges in MS treatment is the unsatisfying subjects' adherence to prescribed treatment. Poor adherence among MS subjects has been found to result from a wide variety of factors among them, lack of injection competence, and adverse events. (3)

Medication Possession Ratio (MPR, i.e. the number of days with a medication supply in the year divided by 365 days) for the once weekly disease-modifying treatment (DMT), Avonex (0.782) was found to be significantly higher than the MPR of daily administrated GA (0.698) (3). A similar MPR for GA treated subjects (0.72) was found in another study of 2,270 GA users. Moreover, similar, higher MPR (0.77) was noted in individuals using the once weekly DMT, Avonex (4). Another study highlighted the connection between MPR and relapse rate in MS patients treated with Copaxone®. In this latter study, patients who achieved an MPR of at least 0.7 had significantly lower odds of relapse than those with MPR thresholds below 0.7, with achievement of a threshold of 0.7, 0.8, or 0.9, associated with an odds ratio of relapse of 0.545, 0.568, and 0.421, respectively (5).

Taken together, these studies stress compliance as an unmet need, which GA Depot will answer by enabling subjects to receive GA once every four weeks, instead of a currently daily or three times a week regimen, as Copaxone®. [redacted]

It is expected that the IM administration of GA Depot every 4 weeks by a healthcare professional will significantly improve treatment of MS subjects by increasing compliance and reducing the injection-site adverse effects due to reduced number of injections.

## 1.3 Name and description of the investigational product

GA Depot [redacted] is being developed for the treatment of RMS.

Placebo for GA Depot [redacted].

GA Depot or Placebo is a lyophilized powder [redacted].

At the Placebo Controlled (PC) period, subjects will be treated once every four weeks with an IM injection of 40mg GA Depot or a placebo. In the Open Label (OL) period all subjects will be treated with GA Depot once every four weeks.

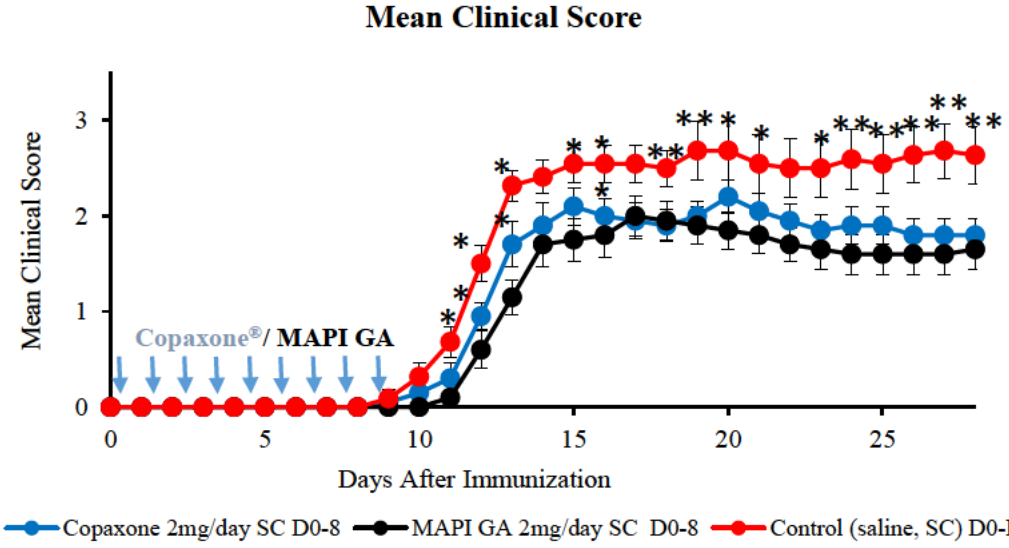
## 1.4 Summary of findings from nonclinical and clinical studies relevant to the trial

### 1.4.1 Preclinical pharmacodynamics – comparison of effects between GA Depot and GA

GA Depot was evaluated in vivo using a Myelin Oligodendrocyte Glycoprotein (MOG) induced experimental autoimmune encephalomyelitis (EAE) in mice. Four studies using MOG induced EAE in mice have been completed.

GA used in the production of GA Depot demonstrated equivalent efficacy to Copaxone® in ameliorating EAE symptoms.

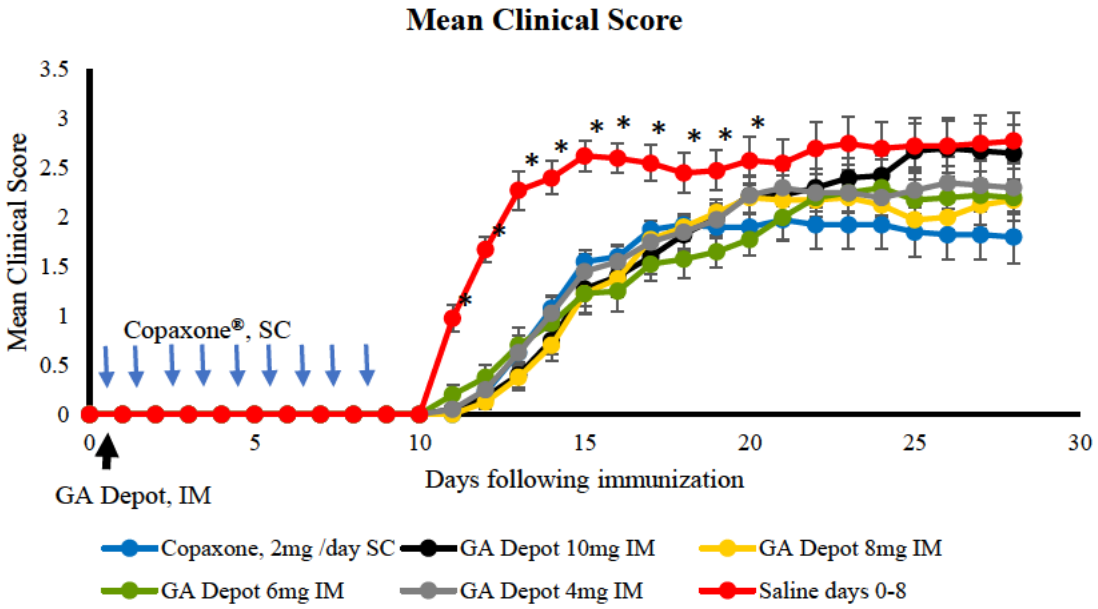
**Comparison of IR GA from Mapi and Copaxone® in Mouse EAE Model**




** 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, +/- standard error.*

A 10mg dose of GA Depot administered once was consistently efficacious in reducing the disease symptoms and in all cases, similar to 2mg Copaxone® administered daily. In dose range finding study, 4mg dose of GA Depot was found to be as efficacious as 10mg dose. Reproducibility of these results was independent of the testing lab used and of the batches of both GA Depot and GA.

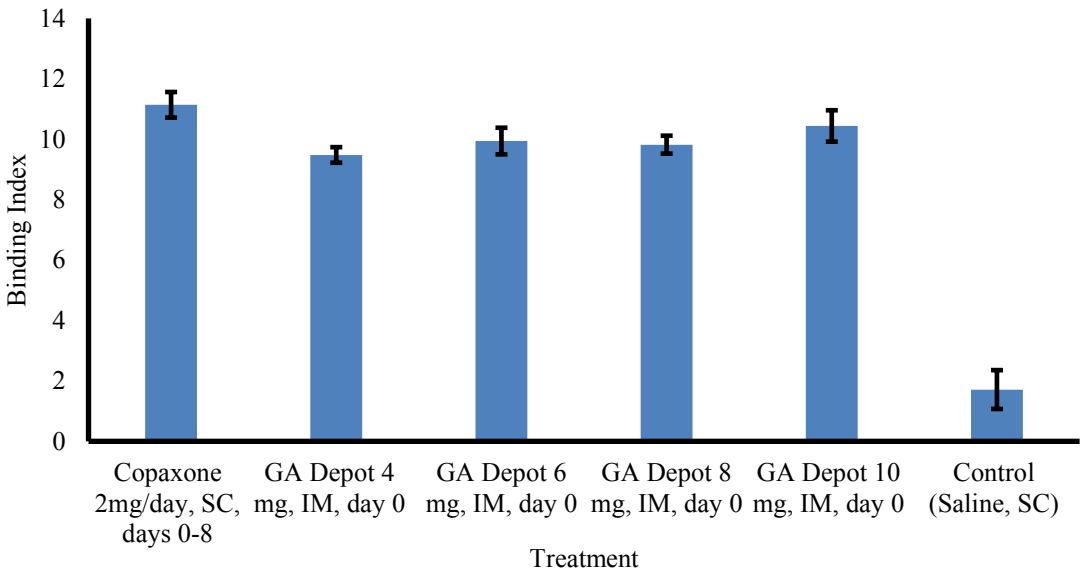
**Dose Ranging of GA Depot in Mouse EAE Model**




**P<0.05 for all treatment groups compared with untreated control, at days 11-19. At day 20 only Copaxone® and GA Depot 6mg IM groups were different from the control. Single Factor ANOVA followed by one-tailed T Test assuming unequal variance. n=20 / group, +/- standard error.*

All studies were performed using a MOG-induced EAE model. This model displays a robust inflammation stage on days 9 to 15 in which demyelination as well as axonal damage is evident. Following this stage, inflammation is usually very moderate. Data from the control group of all studies showed the above dynamic. In all studies, GA Depot showed a clear significant effect of delayed disease onset and amelioration of symptoms, at least as effective as noted for the Copaxone® treated group. Additionally, analysis of Copaxone® or GA Depot treated mice sera reveled that anti-GA antibody titer was similar for mice treated with Copaxone® or with GA Depot, suggesting similar bioavailability. Based on these data we suggest a 1:10 allometric ratio between GA Depot dosages in mice to those in human.

**Immunological response in mice measured by antibodies to GA**




*Serum was isolated from mice in the MOG-EAE study at day 35 following disease induction. Mice were treated with either GA Depot (at 4, 6, 8 or 10mg once) or Copaxone® (2mg/day, days 0 -8). Antibody (Abs) titer was evaluated using an ELISA assay. Results are expressed as Binding Index (BI). n=5*

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

### 1.4.3 Pharmacokinetics (2)

Results obtained in pharmacokinetic studies performed in humans (healthy subjects) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, larger fragments of GA can be recognized by GA-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some, may enter the systemic circulation intact.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

## 1.5 Clinical studies in subjects with MS resulting in approval of GA (2)

Evidence supporting the effectiveness of Copaxone® derives from five placebo-controlled trials, four of which used a Copaxone® dose of 20mg per mL per day and one of which used a Copaxone® dose of 40mg per mL three times per week.

Study 1: This study was performed at a single center. 50 patients were enrolled and randomized to receive daily doses of either GA 20mg subcutaneously, or placebo (GA n=25; placebo n=25). Patients were diagnosed with RRMS by standard criteria and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g. the persistence of the neurological signs for at least 48 hours).

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but 2 other important outcomes were also specified as endpoints: the frequency of relapses during the trial, and the change in the number of attacks compared with the number which occurred during the previous 2 years.

The mean relapse frequency was 0.6/2 years with GA and 2.4/2 years with placebo ($P$=0.005). The results from this study show that there was a statistically significant effect of GA on the number of relapses.

*Study 2*: This study was a multicenter trial of similar design which was performed in 11 US centers. 251 patients (GA n=125; placebo n=126) were enrolled. The primary outcome measure was the mean 2-year relapse rate. The mean number of relapses was 1.19/2 years with GA and 1.68/2 years with placebo ($P$=0.055).

Both studies showed a beneficial effect of GA on relapse rate, and on this basis, GA is considered effective.

*Study 3*: In this study, 481 patients who had recently (within 90 days) experienced an isolated demyelinating event and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either GA 20 mg/day (n=243) or placebo (n=238).(2) The primary outcome measure was time to development of a second exacerbation. Patients were followed for up to 3 years or until they reached the primary endpoint. Secondary outcomes were brain MRI measures, including number of new T2 lesions and T2 lesion volume. Time to development of a second exacerbation was significantly delayed in patients treated with GA compared to placebo (hazard ratio=0.55; 95% confidence interval 0.40 to 0.77). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.9% in the placebo group and 24.7% in the GA group.

Patients treated with GA demonstrated fewer new T2 lesions at the last observation (rate ratio 0.41; confidence interval 0.28 to 0.59; P<0.0001). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with GA (ratio of 0.89; confidence interval 0.84 to 0.94; P=0.0001).

*Study 4*: This was a multinational study in which MRI parameters were used both as primary and secondary endpoints. 239 patients with RRMS (GA n=119; placebo n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least 1 Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for 9 months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the 9 months. The medians of the cumulative number of T1 Gd-enhancing lesions were 11 with GA and 17 with placebo (*P*=0.003).

*Study 5*: This was a double-blind, placebo-controlled, multinational study with a total of 1,404 patients with RRMS randomized in a 2:1 ratio to receive either GA 40mg per mL (n=943) or placebo (n=461) three times a week for 12 months. Patients had a median of 2 relapses in the 2 years prior to screening and had not received any interferon-beta for at least 2 months prior to screening. Baseline EDSS scores ranged from 0 to 5.5 with a median of 2.5. Neurological evaluations were performed at baseline, every three months, and at unscheduled visits for suspected relapse or early termination. MRI was performed at baseline, months 6 and 12, or early termination. A total of 91% of those assigned to GA and 93% of those assigned to placebo completed treatment at 12 months.

The primary outcome measure was the total number of confirmed relapses (persistence of neurological symptoms for at least 24 hours confirmed on examination with objective signs). The effect of GA on several magnetic resonance imaging (MRI) variables, including number of new or enlarging T2 lesions and number of enhancing lesions on T1-weighted images, was also measured at months 6 and 12.

In this study, GA treated subjected had 0.331 relapses during the placebo-controlled phase compared with 0.505 relapses in the placebo group, demonstrating a 34% relative risk reduction (*P*<0.0001). In addition, a reduction of 35% in cumulative number of new or enlarging T2 lesions and a 45% reduction in cumulative number of enhancing lesions on T1-weighted images at months 6 and 12 were noted (*P*<0.0001).

### 1.6 Adverse reactions with GA administration (2) (11)

In all clinical trials with Copaxone® 20 mg/ml, injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving Copaxone®. In controlled studies, the proportion of patients reporting these reactions, at least once, was higher following treatment with Copaxone® (70%) than placebo injections (37%). The most commonly reported injection-site reactions, which were more frequently reported in Copaxone® 20 mg/ml vs. placebo-treated patients, were erythema, pain, mass, pruritus, oedema, inflammation and hypersensitivity.

A reaction, associated with at least one or more of the following symptoms, has been described as the Immediate Post-Injection Reaction: vasodilatation (flushing), chest pain, dyspnoea, palpitation or tachycardia. This reaction may occur within minutes of a Copaxone® injection. At least one component of this Immediate Post-Injection Reaction was reported at least once by 31% of patients receiving Copaxone® 20 mg/ml compared to 13% of patients receiving placebo.

As per Copaxone® FDA label, approximately 16% of patients exposed to COPAXONE 20 mg per mL in the 5 placebo controlled trials compared to 4% of those on placebo, and approximately 2% of patients exposed to COPAXONE 40 mg per mL in a placebo-controlled trial compared to none on placebo, experienced a constellation of symptoms that may occur immediately (within seconds to minutes, with the majority of symptoms observed within 1 hour) after injection and included at least two of the following: flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, and urticaria.

All adverse reactions, which were more frequently reported in Copaxone® 20 mg/ml vs. placebo-treated patients, are presented in the table below. This data was derived from four pivotal, double-blind, placebo-controlled clinical trials with a total of 512 patients treated with Copaxone® 20 mg/ml and 509 patients treated with placebo for up to 36 months. Three trials in relapsing-remitting MS (RRMS) included a total of 269 patients treated with Copaxone® 20 mg/ml and 271 patients treated with placebo for up to 35 months. The fourth trial in patients who have experienced a first clinical episode and were determined to be at high risk of developing clinically definite MS included 243 patients treated with Copaxone® 20 mg/ml and 238 patients treated with placebo for up to 36 months.

Most frequently reported adverse reactions in Copaxone® 20 mg/ml vs. placebo pivotal trials

| System Organ Class (SOC) | Very Common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) |
|---|---|---|---|
| Infections and infestations | Infection, Influenza | Bronchitis, Gastroenteritis, Herpes Simplex, Otitis Media, Rhinitis, Tooth Abscess, Vaginal Candidiasis* | Abscess, Cellulitis, Furuncle, Herpes Zoster, Pyelonephritis |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | | Benign Neoplasm of Skin, Neoplasm | Skin Cancer |
| Blood and lymphatic system disorders | | Lymphadenopathy* | Leukocytosis, Leukopenia, Splenomegaly Thrombocytopenia, Lymphocyte Morphology Abnormal |
| Immune system disorders | | Hypersensitivity | |
| Endocrine disorders | | | Goitre, Hyperthyroidism |
| Metabolism and nutrition disorders | | Anorexia, Weight Increased* | Alcohol Intolerance, Gout, Hyperlipidaemia, Blood Sodium Increased, Serum Ferritin Decreased |
| Psychiatric disorders | Anxiety*, Depression | Nervousness | Abnormal Dreams, Confusional State, Euphoric Mood, Hallucination, Hostility, Mania, Personality Disorder, Suicide Attempt |
| Nervous system disorders | Headache, | Dysgeusia, Hypertonia, Migraine, Speech Disorder, Syncope, Tremor* | Carpal Tunnel Syndrome, Cognitive Disorder, Convulsion, Dysgraphia, Dyslexia, Dystonia, Motor Dysfunction, Myoclonus, Neuritis, Neuromuscular Blockade, Nystagmus, Paralysis, Peroneal Nerve Palsy, Stupor, Visual Field Defect |
| Eye disorders | | Diplopia, Eye Disorder* | Cataract, Corneal Lesion, Dry Eye, Eye Haemorrhage, Eyelid Ptosis, Mydriasis, Optic Atrophy |
| Ear and labyrinth disorders | | Ear Disorder | |
| Cardiac disorders | | Palpitations*, Tachycardia* | Extrasystoles, Sinus Bradycardia, Tachycardia Paroxysmal |
| Vascular disorders | Vasodilatation* | | Varicose Vein |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea* | Cough, Rhinitis Seasonal | Apnoea, Epistaxis, Hyperventilation, Laryngospasm, Lung Disorder, Choking Sensation |
| Gastrointestinal disorders | Nausea* | Anorectal Disorder, Constipation, Dental Caries, Dyspepsia, | Colitis, Colonic Polyp, Enterocolitis, Eructation, Oesophageal Ulcer, |

| System Organ Class (SOC) | Very Common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) |
|---|---|---|---|
| | | Dysphagia, Faecal Incontinence, Vomiting* | Periodontitis Rectal Haemorrhage, Salivary Gland Enlargement |
| Hepatobiliary disorders | | Liver Function Test Abnormal | Cholelithiasis, Hepatomegaly |
| Skin and subcutaneous tissue disorders | Rash* | Ecchymosis, Hyperhidrosis, Pruritus, Skin Disorder*, Urticaria | Angioedema, Dermatitis Contact, Erythema Nodosum, Skin Nodule |
| Musculoskeletal and connective tissue disorders | Arthralgia, Back Pain* | Neck Pain | Arthritis, Bursitis, Flank Pain, Muscle Atrophy, Osteoarthritis |
| Renal and urinary disorders | | Micturition Urgency, Pollakiuria, Urinary Retention | Haematuria, Nephrolithiasis, Urinary Tract Disorder, Urine Abnormality |
| Pregnancy, puerperium and perinatal Conditions | | | Abortion |
| Reproductive system and breast disorders | | | Breast Engorgement, Erectile Dysfunction, Pelvic Prolapse, Priapism, Prostatic Disorder, Smear Cervix Abnormal, Testicular Disorder, Vaginal Haemorrhage, Vulvovaginal Disorder |
| General disorders and administration site conditions | Asthenia, Chest Pain*, Injection Site Reactions*§, Pain* | Chills*, Face Oedema*, Injection Site Atrophy♣, Local Reaction*, Oedema Peripheral, Oedema, Pyrexia | Cyst, Hangover, Hypothermia, Immediate Post-Injection Reaction, Inflammation, Injection Site Necrosis, Mucous Membrane Disorder |
| Injury, poisoning and procedural complications | | | Post Vaccination Syndrome |

** More than 2% (>2/100) higher incidence in the Copaxone® treatment group than in the placebo group. Adverse reaction without the * symbol represents a difference of less than or equal to 2%.*
*§ The term 'Injection site reactions' (various kinds) comprises all adverse events occurring at the injection site excluding injection site atrophy and injection site necrosis, which are presented separately within the table.*
*♣ Includes terms which relate to localized lipoatrophy at the injection sites.*
*In the fourth trial noted above, an open-label treatment phase followed the placebo-controlled period (see section 5.1). No change in the known risk profile of Copaxone® was observed during the open-label follow-up period of up to 5 years.*

The safety of Copaxone® 40 mg/ml was assessed based on a double-blind, placebo-controlled clinical trial in RRMS patients with a total of 943 patients treated with Copaxone® 40 mg/ml three times per week, and 461 patients treated with placebo for 12 months.

In general, the kind of adverse drug reactions seen in patients treated with Copaxone® 40 mg/ml administered three times per week were those already known and labelled for Copaxone® 20 mg/ml administered daily. In particular, adverse injection site reactions (ISR) and immediate post-injection reactions (IPIR) were reported at lower frequency for Copaxone® 40 mg/ml administered three times per week than for Copaxone® 20 mg/ml administered daily (35.5 % vs. 70 % for ISRs and 7.8 % vs. 31 % for IPIRs, respectively).

Injection site reactions were reported by 36% of the patients on Copaxone® 40 mg/ml compared to 5% on placebo. Immediate post-injection reaction was reported by 8% of the patients on Copaxone® 40 mg/ml compared to 2% on placebo.

### 1.7 Drug interactions (2)

Interactions between Copaxone® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of Copaxone® with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. Copaxone® has not been formally evaluated in combination with interferon beta.

### 1.8 Clinical study in subjects with MS with GA Depot

GA Depot was tested in a first-human trial entitled "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 80mg or 40mg glatiramer acetate (GA Depot) in subjects with relapsing remitting multiple sclerosis (RRMS)". This non-IND Phase IIa trial (ClinicalTrials.gov identifier: NCT02212886) was approved by the Israeli Ministry of Health and by the IRBs of 8 medical centers and was initiated in November 2014. The one-year trial was completed in May 2017 and the extension of the study is ongoing.

GA Depot has been administered to 25 subjects in the RRMS phase IIa study, who received at least 1 injection within the study framework; 12 subjects in the 80mg group and 13 subjects in the 40mg group. 13 Subjects continued to the extension study, with monthly 40mg GA Depot administration.

Safety and tolerability of GA Depot was the primary endpoint in the phase IIa one-year core study.

The most common related adverse events (AEs) recorded during the phase IIa one-year core study were mild injection site reactions (ISRs). These AEs were reported more often in the 80mg group. The most commonly reported ISRs were pain, haematoma, hypersensitivity, injection site induration, inflammation, swelling, injection site mass, oedema, pruritus, rash, warmth and erythema. In some cases, moderate pain for several days was reported. In addition, in one patient cellulitis was reported and in three other patients abscess at injection site, were reported.

Most common AEs other than ISRs, related or unrelated to GA Depot recorded during the study were also mild. AEs other than ISRs reported in 10% of the patients or more in any of the treatment groups were as follows: nausea, asthenia, fatigue, pain, urinary tract infection, pyrexia, arthralgia, dizziness, headache, back pain, CPK elevation, rash and pain in the extremity.

Overall no unexpected safety issues were noted with GA Depot.

[redacted]

Efficacy secondary endpoints during core study were defined as follows:

- Changes from baseline to end of treatment visit of the number of enhancing lesions and new lesions images of brain MRI.
- Change from baseline to end of treatment visit of Expanded Disability Status Scale (EDSS) score.
- Relapse rate detected during the study compared to relapse rate observed in the 12 months prior to study start when subjects were treated by Copaxone®.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

## 1.9 Summary of known and potential risks and benefits to human subjects

Long-term treatment with GA has been safe and generally well tolerated in patients with RMS at daily doses of up to 20mg/day or three times a week at a dose of 40mg when administered subcutaneously. At the same time, GA was effective in reducing MS relapse rates.

It is expected that the IM administration of GA Depot every 4 weeks by a healthcare professional will significantly improve treatment of MS patients by increasing compliance and will reduce the annual injection-site reactions due to reduced number of injections.

Thus, the benefits outweigh potential risks known at this stage of development.

## 1.10 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s)

Dose selection is based on the following information:

Pre-clinical: GA Depot is at least as effective as Copaxone® in EAE mice model, in a dose range corresponding to 40mg -100mg GA Depot human dose, based on the proposed 1:10 allometric ratio (see section #1.4.1 above).

The histopathological features of GA Depot injection sites are similar to those reported in other FDA-approved PLGA-based depot products. A clear trend of recovery was noted at all injection sites. The lesions observed in the low dose GA Depot group (equivalent to 40mg human dose) were milder compared with the lesions observed in the high dose GA Depot group, supporting the 40mg dose choice.

The efficacy in the small cohort Phase IIa one-year study suggests similar efficacy results for both dosage strengths of GA Depot (80mg and 40mg). Patients remain stable with regards to the three independent efficacy parameters: relapse rate, MRI scans and EDSS score, suggesting at least as good efficacy as marketed Copaxone® (see section 1.8 for full efficacy results). Both 40mg and 80mg dosage strengths are generally safe and tolerable; however, the 40mg dosage has shown statistically significant better safety and tolerability (see section 1.8 for full safety data). As safety and tolerability profiles are imperative for RMS patients due to the chronic nature of the therapy, a dose of 40mg GA Depot once every four weeks is preferred.

Taking all of the above into consideration, the 40mg dose once every four weeks regimen is selected for phase III clinical development and is expected to be as efficient as Copaxone®, safe, and with a better compliance profile in the long term, in comparison to Copaxone®.

## 1.11 GCP compliance statement

This study will be conducted in compliance with the protocol, national laws, international guidelines, and the valid version of the Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP).

The Sponsor and/or its agents will systematically control the essential documents generated during this trial. All phases of the trial will be monitored by the Sponsor and/or its agents. All clinical study monitoring visits and inspections will be followed by internal reports and corrective actions, if needed. Follow-up letters will be forwarded to sites after all clinical visits.

## 1.12 Description of the population to be studied

The study will enroll male and female subjects between the age of 18 and 55 diagnosed with RMS who comply with the inclusion and exclusion criteria as specified in this protocol. For inclusion and exclusion criteria see Section 4.

# 2 TRIAL OBJECTIVES AND PURPOSE

This study is designed to assess the efficacy, safety and tolerability of GA Depot as compared to placebo in subjects with RMS.

In addition, the study is designed to assess the long-term safety and tolerability of GA Depot, for a period of up to 104 weeks.

# 3 TRIAL DESIGN

## 3.1 Primary and secondary endpoints

This is a Phase III study in which GA Depot 40mg or matching placebo are administered IM to subjects with RMS at a 4-week intervals for 52 weeks of treatment (in the PC period). At the OL period, all subjects will be treated with GA Depot.

Primary Efficacy Endpoint:

Annualized Relapse Rate (ARR) during the 52 weeks of the PC period as derived from the total number of confirmed relapses.

Secondary Efficacy Endpoints:

All secondary endpoints will utilize the data collected only during the PC Period of the study.

1. Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline.
2. Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline.
3. Change from baseline to Week 52 in hyperintense T2-lesion volume.
4. Change from baseline to Week 52 in enhancing T1-lesion volume.

[redacted]

## 3.2 Type/design of trial and schematic diagram of trial design, procedures, and stages

A multinational, multicenter, randomized, Phase III, parallel group, placebo controlled study. Subjects and sites will remain blinded to PC treatment assignment during both PC and OL Periods of the study.

See Section 16.1 for the schedule of procedures.

**Procedures/evaluation criteria**

*Demographic data and medical history*: This information will be collected at screening to ensure suitability according to the inclusion and exclusion criteria. MS history (including

number of documented relapses and EDSS from the two years prior to screening and date of last MRI with Gd enhancing lesions).

*Physical examination:* A full physical examination will be performed to ensure suitability according to the inclusion and exclusion criteria at screening and in order to document the health status will be performed at [redacted]

*Vital signs:* Vital signs (blood pressure [BP], heart rate, and body temperature), will be measured in a sitting position after resting for about 5 minutes, at [redacted].

*Phone call:* will be scheduled between 4-7 days following the first GA Depot or matching placebo injection to assess the subjects' well-being.

*12-lead ECG:* The ECG will be recorded at [redacted].

*MRI brain scan:* MRI scans will be conducted during screening period, 24 weeks, 52 weeks and at termination (104 weeks). MRI will be performed not less than 1 month after last treatment with steroids. MRI data will be conveyed to the central reading facility. [redacted].

*Neurological evaluations:* EDSS scores and MSFC assessments will be recorded at [redacted].

During the OL period EDSS and MSFC will be recorded at [redacted]

[redacted]

*Laboratory investigations:* Laboratory testing will be performed at [redacted]

- [redacted]
- [redacted]
- [redacted]

Serum samples will be collected at [redacted]

When, in the subject's best interest, additional tests may be performed at the discretion of the investigator to ensure their good health.

[redacted]

**Handling of blood samples**

During the study, laboratory testing will be performed according to the study schedule and at a central appropriately accredited laboratory. At screening/baseline, the results will be used to assess subject's eligibility and will be filed in the subject's chart. If clinically indicated, the investigator may use the local laboratory for any laboratory tests deemed necessary.

The investigator will be required to use clinical judgment when determining the clinical significance of out-of-range laboratory findings. [redacted]

[redacted]

[redacted]

### 3.3 Randomization/blinding

This is a multinational, multicenter, randomized, double blind - placebo controlled study. In the PC period, a total of [redacted] were originally planned to be randomized into this study to receive treatment with GA Depot or with matching placebo using a 1:1 randomization scheme [redacted] Following the conduct of the pre-planned blinded, non-comparative, sample size reassessment the study size was increased to [redacted]. During the OL period all subjects will be treated with GA Depot.

### 3.4 Expected duration of subject participation, sequence, and duration of all trial periods including follow-up

The study duration in an individual subject will be up to 112 weeks, consisting of 4 weeks of screening evaluation (weeks -4 to 0), followed by a 52-week PC period, a follow up visit at week 56 for those subjects electing not to continue to the OL period and for those continuing on the OL period, there will be a 52-week OL period and a follow-up visit at week 108.

Schematic description of the trial schedule:

| Treated by | Screening (weeks -4 to 0) | Placebo Controlled (PC) period (weeks 0-52) | Open Label (OL) period (weeks 52 to 104) | Follow Up (weeks 105 to 108) |
|---|---|---|---|---|
| **GA Depot group** | 4 weeks | [redacted] administrations, during the PC period [redacted] | [redacted] administrations, to all subjects treated in the PC period (both on GA Depot and Placebo Depot) | 4 weeks |
| **Placebo Depot** | 4 weeks | [redacted] administrations, during the PC period [redacted] | No subjects will be treated with placebo | 4 weeks |

See also detailed description in Table 16-1

## 3.5 Stopping rules/discontinuation for the entire study

The study may be stopped or discontinued for the following reasons:

- The DMC or the Principal Investigator can recommend to halt the clinical trial, The Sponsor can decide that the safety profile of the IP justifies discontinuation of the study.
- The Sponsor considers the applied doses of the IP to be no longer relevant or has decided to halt the clinical trial.
- Data not known before become available and raise concern with respect to the safety of the IP so that continuation would pose potential risks to the subjects.

## 3.6 Accountability procedures for investigational products including placebo

The investigational product (IP) (GA Depot) will be shipped directly to the respective research sites. Procedures will comply with International Conference on Harmonization – Good Clinical Practice (ICH-GCP)/FDA guidelines for shipment of IP and will follow the Standard Operating Procedures of the Contract Research Organization (CRO). All essential documentation for drug shipment will have to be received and approved prior to IP being shipped. The amount of IP to be shipped to the study sites will depend on the expected number of subjects to be enrolled at each site.

The clinical monitor or designee will verify that the receipt, use, and return of the IP at the trial sites are controlled and documented adequately. Empty vials will be kept at the site for record reconciliation by the clinical study monitor or designee. The IP will be securely stored, with an authorized person dispensing it only for this study. This will be clearly documented in the drug accountability log which will be monitored. All unused product will be accounted for on a drug accountability log. Return or destruction will take place only after verification and as authorized by the Sponsor or its representative.

### 3.7 Maintenance of trial treatment randomization codes and procedures for breaking codes

All subject treatment details and randomization codes will be allocated and maintained by the Medidata RTSM system.

In case of a serious adverse event when the study drug assignment is needed to make treatment decisions for the subject, the investigator may unblind the subject's drug assignment via the RTSM system. The Sponsor should be notified of the event prior to breaking of the code, if possible. If this is not possible, the Sponsor should be notified afterwards, and the subject's drug code assignment should not be revealed. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the source documents.

The process for breaking the code is described in the study pharmacy manual.

### 3.8 Identification of data to be recorded directly on the CRFs and to be considered source data

No data will be entered directly in the CRF.

### 3.9 MRI Central Reading

MRI scans will be transferred electronically to [redacted] for central reading. In order to ensure standardization of the MRI scans, each participating site will be provided with the MRI manual, be trained on MRI requirements and qualified by [redacted] following transfer of a Dummy run MRI. For the Dummy MRI run, either a healthy volunteer or an MS subject can be candidates. Prior to undergoing the dummy run MRI, candidates will sign the relevant written informed consent.

# 4 SELECTION AND WITHDRAWAL OF SUBJECTS

The selection criteria are chosen to ensure that subjects with specific risks for administration of the IP and/or subjects with conditions which may have an impact on the aims of the study are excluded.

## 4.1 Subject inclusion criteria

Subjects must fulfill all of the following criteria before being included in the study:

1. Adult subjects, between 18-55 years of age, inclusive.
2. Subjects able to provide signed written informed consent.
3. Subjects must be willing and able to comply with the protocol requirements for the duration of the study.
4. MS diagnosis fulfilling the 2017 McDonald Criteria.
5. Subjects should be ambulatory with an EDSS score of 0-5.5 at screening and baseline visits. EDSS score will be determined by a separate, blinded trained EDSS rater[4].
6. Subjects should be relapse free and neurologically stable from one month before screening visit and from screening visit to the baseline visit.
7. No systemic corticosteroid treatment or ACTH within one month prior to screening visit.
8. Subjects must have experienced at least one of the following:
   - At least one documented relapse in the 12 months prior to screening,
   - At least two documented relapses in the 24 months prior to screening,
   - One documented relapse between 12 and 24 months prior to screening with at least one documented T1-Gd enhancing lesion in MRI performed within 0-12 months before screening.
9. Women capable of child bearing must have a negative urine pregnancy test at screening and baseline visit and use an adequate contraceptive method throughout the study. Acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptives, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy or double barrier method (condom and diaphragm with spermicide).

## 4.2 Subject exclusion criteria

Subjects are to be excluded from the study if they display any of the following criteria:

1. Use of experimental / investigational drug, and / or participation in drug clinical studies within the 6 months prior to screening.
2. Any off-label drug use for MS treatment such as high dose simvastatin and biotin within 6 months prior to screening.
3. Previous use of immunosuppressant including Mitoxantrone or Alemtuzumab, cladribine or any other cytotoxic agent within 5 years.
4. Previous use of natalizumab or any anti-B cell agent within 9 months prior to screening.
5. Previous use of Fingolimod or any other sphingosine-1-phosphate receptor modulator, Dimethyl fumarate, Diroximel Fumarate (DRF), or Monomethyl fumarate within 2

[redacted]

months prior to screening. Subjects will be excluded if they do not have a lymphocyte count of above 1,000 /$mm^3$ at screening.

6. Previous use of Teriflunomide within 12 months if no accelerated elimination procedure was used.
7. Previous treatment with immunomodulators (including IFNβ 1a and 1b, and IV Immunoglobulin (IVIg) within 2 months prior to screening.
8. Previous use of GA or any other glatiramoid.
9. Chronic (more than 30 consecutive days) systemic (IV, PO or IM) corticosteroid treatment within 6 months prior to screening visit.
10. Previous total body irradiation or total lymphoid irradiation.
11. Previous stem-cell treatment, autologous bone marrow transplantation or allogeneic bone marrow transplantation.
12. Subjects with a clinically significant or unstable medical, psychiatric, or surgical conditions that would preclude safe and complete study participation, as determined by medical history, physical exams, ECG and/or abnormal laboratory tests; and or subjects with an increased risk of serious Covid-19 related morbidity. Such conditions may include hepatic, renal or metabolic diseases, systemic disease, acute infection, current malignancy or recent history (5 years) of malignancy, major psychiatric disorder, history of drug and/or alcohol abuse and allergies that could be detrimental according to the investigator's judgment.
13. Subjects who have >10 T1-Gd enhancing lesions at screening
14. A known history of sensitivity to Gadolinium.
15. Inability to successfully undergo MRI scanning.
16. Pregnant or breast-feeding women.
17. Abnormal renal function (serum creatinine >1.5xULN or creatinine clearance <60 ml/min).
18. Abnormal liver function (transaminases >2xULN).
19. History of any anaphylactic reaction and/or serious allergic reaction following a vaccination, a proven hypersensitivity to any component of the study article (e.g., GA, Polyglactin, PVA).
20. Positive testing or a history of positive testing for syphilis, HIV, hepatitis, or tuberculosis.
21. Known or suspected history of drug or alcohol abuse.
22. Subjects diagnosed with any other than MS systemic autoimmune disease that may impact the CNS with MS like lesions such as Sarcoidosis, Sjögren's syndrome, Systemic Lupus Erythematosus (SLE), Lyme disease, APLA syndrome, etc. Subjects with stable local/organ autoimmune disease such as psoriasis, Cutaneous Lupus erythematosus, thyroiditis (Hashimoto's, Grave's) etc. may be considered eligible upon the PI's discretion.
23. Any CNS disorder other than MS that may jeopardize the subject's participation in the study.
24. Uncontrolled diabetes.
25. Subjects with clotting disorders or receiving treatment with anticoagulants.[5]

[5] The use of antiplatelet agents is permitted

### 4.3 Subject withdrawal criteria and procedures

Subjects may be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative, at any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage consequently. The investigator should make reasonable efforts to ascertain the reason(s), while fully respecting the subject's rights.
- If, in the investigator's opinion, continuation of study would be harmful to the subject's well-being.
- At the specific request of the Sponsor.
- Violation of the inclusion/exclusion criteria (for details, see below).
- Non-compliance with the study conditions or instructions such that no data can be gathered about safety endpoints or such that the subject places him/herself at unreasonable risk in the opinion of the investigator.
- Data not known before become available and raise concern with respect to the safety of the investigational product (IP) so that continuation would pose potential risks to the subject.
- Refusal to sign the re-consent form.
- Pregnancy.
- Lost to follow up/failure to return. A patient should only be designated as lost to follow up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc.)
- In case a subject has one or more of the following:
  1. Abnormal blood tests AST > 5xULN and /or ALT >5xULN.
  2. Creatinine > 1.5xULN.
  3. Lymphocytes count <200/µl.

  In these cases, the treatment should be temporarily interrupted for 2 weeks. It is to be at the discretion of the investigator if after re-evaluation and validation that the subject's blood tests are within normal range, the subject will continue his/her participation in the study.
- In case of an unexpected new neurological finding/s in MRI scans that are not MS related, it is to be at the discretion of the investigator if the subject will continue his/her study participation.

A subject who discontinues study participation prematurely for any reason after randomization but **before administration of any IP** will not be replaced. These subjects need no further follow-up of any sort in the framework of this study.

If a subject is discovered to be in violation of one or more of the inclusion/exclusion criteria **after administration of study drug**, the case will be brought to the attention of the Sponsor with no delay and a joint decision will be made concerning the subject's participation in the study. **If the subject's participation will be terminated**, such subjects should still undergo the safety evaluations mandated by the protocol, but without the efficacy assessments, unless the subject withdraws his/her consent altogether when the violation is discovered (in which case efforts will be made for the subject to perform at least an end-of-study safety evaluation). These subjects will be part of the safety population, but not of the efficacy population.

**Handling subjects' discontinuation after administration of study drug**

Subjects discontinuing the trial, either due to the investigator's decision, or a subject's own decision will undergo, whenever possible, a complete end-of-study evaluation (as planned at

the EoT visit) including a physical examination, vital signs, MRI brain scan, EDSS score, and laboratory tests.

All subjects who withdraw their consent due to AEs or laboratory abnormalities will be followed up at suitable intervals, whenever possible, to evaluate the course of the AE or laboratory abnormalities and to ensure reversibility or stabilization if possible. The subsequent outcomes of these events will be recorded on the CRF if the data is available.

Reasons for discontinuation will be documented in the CRFs in all cases.

**Premature termination of study/closure of center**

The Sponsor has the right to close this study or the study site, at any time, after discussion between the involved parties. The site's Ethics Committee/IRB must be informed. Should the study/site be closed prematurely, all study materials (except documentation that must remain stored at site) must be returned to the Sponsor. The investigator will retain all other documents until a notification is given by the Sponsor for destruction or 15 years whichever occurs first. In any case, in accordance to the applicable regulatory guidelines.

# 5 TREATMENT OF SUBJECTS

## 5.1 Treatments to be administered

### 5.1.1 Formulation and dosing of study drug

GA Depot is a combination of GA encapsulated in extended-release microspheres for injection and diluent for parenteral use.

[redacted]

The diluent for parenteral use is sterile water for injection. The microspheres are suspended in the diluent prior to injection.

**Test treatment**

[redacted]

Dosage schedule: at the PC period, each subject will receive 40mg of GA Depot or placebo administered IM once every 4 weeks, 13 times for a total of 52 weeks of treatment. At the OL period, all subjects will receive GA Depot IM once every 4 weeks for additional 52 weeks.

### 5.1.2 Formulation and dosing of control product

Placebo formulation is identical to that of GA Depot, with no GA. Administration of placebo will be performed as described for GA Depot.

## 5.2 Storage, packaging, and labeling information

**Storage**

[redacted]

The Sponsor will provide each site with study medication sufficient for the number of subjects the site is planning to enroll. The pharmacist or designee will receive the shipment/s of the study medication and will store it as per the local procedures at the site and the applicable regulatory procedures. The pharmacist or the study staff will confirm receipt of study drug.

Study medication will be stored in a refrigerator at 2°C to 8°C, protected from light.

The storage location should be secure and locked and accessible to authorized study staff personnel until allocated to a subject. Study medication accountability records (subject and site accountability records) will be maintained and updated for all study medication.

The unused and/or expired study medication will be returned for central destruction or destroyed according to local regulations. A copy of the accountability records will be provided to the Sponsor and will be attached to a destruction certificate.

[redacted]

**Labeling**

Study medication will be packaged by the Sponsor or its agent.

Study medication will be labeled according to the current International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements.

The information on the labels will be in English and in additional languages according to local regulations.

## 5.3 Study medication preparation procedure

After completion of the screening and baseline assessments, GA Depot or matching placebo will be administered [redacted] at a 4-weeks interval for a total of 52 weeks of treatment during the PC period. During the OL period all subjects will receive GA Depot at a 4-weeks interval for an additional 52 weeks.

The drug product (GA Depot or matching placebo) and diluent are brought to room temperature[redacted]

Alternating injection site for each subsequent injection. Injection sites are the gluteus muscle or deltoid muscle. Body habitus should be assessed prior to each injection for each subject to assure that needle length is adequate for an intramuscular administration. GA Depot or matching placebo must be administered by study personnel as detailed in the delegation form. Study personnel will document injection site, and subject reported (if any) discomfort during the injection.

GA Depot or matching placebo MUST NOT be administered intravenously or subcutaneously. See GA Depot injection guidelines for the full study drug procedure instructions.

## 5.4 Medications before and/or during the trial

All MS medications taken up to 2 years and all concomitant medications taken up to one month prior to screening will be recorded.

Topical and inhaled steroids are allowed at the discretion of the Treating Neurologist for indications other than MS.

Use of the following MS treatments are NOT allowed concomitantly with the study drug during the course of the study:

- Systemic corticosteroids except for the treatment of investigator-determined relapses, if considered appropriate by the PI.
- ACTH.
- Any immuno-modulating treatment (e.g. interferon beta, natalizumab or other monoclonal antibody therapy, etc).
- Immunosuppressive medication (e.g. cyclosporine, azathioprine, methotrexate cyclophosphamide, mitoxantrone, cladribine).
- Plasmapheresis.
- Vaccinations except for annual flu vaccines and the need for tetanus or other vaccine that according to the PI is required by the participating subject.
- Any other investigational drug.

### 5.5 Monitoring of subject compliance

Study medication will be administered by study medical staff. Subject compliance will be monitored and followed by study staff as detailed in Section 6.2.

### 5.6 Definition of a relapse

In this study, relapse will be defined as:

1. [redacted]

### 5.7 Re-consent Criteria:

In case of a [redacted] the following actions will be taken:

- The subject will be reminded of the currently available MS medications/treatments and the opportunity to terminate his/her participation in the study.
- The subject will be requested to re-sign an informed consent form if he/she chooses to continue to participate in the study, in the same treatment assignment.

# 6 ASSESSMENTS OF EFFICACY

## 6.1 Specification of efficacy parameters

Primary Efficacy Endpoint:

Annualized Relapse Rate (ARR) during the 52 weeks of the PC period as derived from the total number of confirmed relapses.

Secondary Efficacy Endpoints:

All secondary endpoints will utilize the data collected only during the PC Period of the study.

1. Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline.
2. Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline.
3. Change from baseline to Week 52 in hyperintense T2-lesion volume.
4. Change from baseline to Week 52 in enhancing T1-lesion volume.

12. [redacted]

[redacted]

[redacted]

## 6.2 Methods of timing for assessing, recording, and analyzing of efficacy parameters

[redacted]

[redacted]

[redacted]

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[redacted]

[6] Antibody testing will be done at EoT for subjects completing the PC period, and not at early termination visit.

**Unscheduled visits may be performed as needed.**

The date and reason for the unscheduled visit will be recorded.
The reasons for the unscheduled visit may be:

- [redacted]

[redacted]

**Clinical Trial Data Monitoring Committee (DMC)**

An independent Clinical Trial Data Monitoring Committee (DMC) will be established according to the FDA's Guidance (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees; 2006). [redacted]

**Patient reported outcomes**

[redacted]

# 7 ASSESSMENT OF SAFETY

## 7.1 Specification of Safety and Tolerability Outcome Measures

The following safety and tolerability outcome measures will be assessed at the time-points indicated in the study flow chart (Table 16-1):

Safety and tolerability outcome measures will be evaluated at the end of the PC period:

Safety:

- Adverse events.
- Vital signs.
- ECG findings.
- Laboratory parameters.

Tolerability:

- The frequency, incidence and severity of post injection site reactions (ISRs).
- The frequency and incidence of immediate post injection systemic reactions.

The long-term safety and tolerability will also be evaluated at the end of the OL period for the treatment duration of up to 104 weeks.

## 7.2 Methods of timing for assessing, recording, and analyzing of safety parameters

See Section 6.2.

## 7.3 Recording and reporting adverse events and intercurrent illnesses

### 7.3.1 Adverse event

Recording of adverse events will begin after subjects signed the Informed Consent Form and throughout the study, until 30 days following the last administration date and at follow up visit.
All adverse events should be reviewed and updated at each subsequent visit and during any phone contact with the subjects.

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject. The adverse event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Abnormal laboratory findings will be considered an AE if it is associated with clinical signs or symptoms and or if it is considered to be of clinical significance by the treating physician.

MS relapses will not be recorded as adverse events. MS relapses will be validated by the treating physician within no more than 2 weeks from onset of MS relapse symptoms and will be captured in the CRF in the MS relapse form.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An adverse event occurring during a participation of a subject in a clinical research.

- An adverse event occurring from an overdose whether accidental or intentional.
- An adverse event occurring from drug abuse.
- An adverse event occurring from drug withdrawal.

An adverse event where there is a reasonable possibility that the event occurred purely as a result of the subject's participation in the study (e.g. adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an adverse event if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria for a "serious" adverse event, it must be recorded and reported as such.

### 7.3.2 Serious adverse event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

**Life-threatening:** The term "life-threatening" in the definition of "serious adverse event" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

**Hospitalization:** Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least 1 of the following exceptions is met:

- The admission results in a hospital stay of less than 24 hours, or,
- The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study), or,
- The admission is not associated with an adverse event (e.g. social hospitalization for purposes of respite care).
- The admission is for treating a relapse event.

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

**Disability** means a substantial disruption of a person's ability to conduct normal life's functions.

**Important medical event:** Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction

Terminology – Critical Terms List". These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

### 7.3.3 Unexpected adverse event

An unexpected adverse event is any adverse drug event in which the specificity or severity is not consistent with the current Investigator's Brochure (or package insert for marketed products). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events.

### 7.3.4 Causality/Relatedness of adverse events to investigational product

The assessment of the relatedness of an adverse event to the administration of IP is a clinical decision based on all available information at the time of the completion of the case report form.

The causality categories are as follows:

- Unrelated.
- Unlikely related (event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable but not impossible), disease or other drugs provide plausible explanations).
- Possibly related (event or laboratory test abnormality, with reasonable time relationship to drug intake, could also be explained by disease or other drugs).
- Probably related (event or laboratory test abnormality, with reasonable time relationship to drug intake, unlikely to be attributed to disease or other drugs).
- Related (event or laboratory test abnormality, with plausible time relationship to drug intake, event cannot be explained by disease or other drugs).
- Unknown.

Factors to be considered in assessing the relationship of the adverse event to IP include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects' response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

### 7.3.5 Severity of the adverse event

The severity of adverse events should be graded as follows:

- Mild – usually transient in nature and generally not interfering with normal activities.
- Moderate – sufficiently discomforting to interfere with normal activities.
- Severe – prevents normal activities.

### 7.3.6 Adverse event documentation

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

## 7.4 Reporting of serious adverse events/pregnancy

Serious adverse events, including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent and until 30 days after last study drug dose administration must immediately (within 24 h of the investigator's awareness) be reported to the Medical Monitor and the Sponsor as detailed in the study file using the adequate forms. Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the Medical Monitor or designee.

When required, and according to local law and regulations, serious adverse events may be reported to the IRBs/Ethics Committee(s) and regulatory authorities.

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to the Medical Monitor or designee within the same timelines and study drug should be permanently discontinued. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

## 7.5 Type and duration of follow-up of subjects after adverse events

If possible, all subjects will be followed up until the AE/SAE has been resolved or stabilized.

# 8 STATISTICAL METHODOLOGY

This multicenter, randomized, double blind, placebo-controlled study is designed to assess the efficacy, safety and tolerability of a long-acting IM injection of 40mg GA Depot administrated every four weeks as compared to placebo in subjects with RMS a double-blind setting of 52 weeks. In addition, the study is designed to assess the long-term safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered every four weeks for a period of up to 104 weeks.

A total of [redacted] were originally planned to be randomized into this study to receive treatment with GA Depot or with matching placebo employing a 1:1 randomization scheme [redacted]). Following the conduct of the pre-planned blinded, non-comparative, sample size reassessment the study size was increased to [redacted].

The overall significance level for this study will be 5% using two-tailed tests. The gatekeeping approach will be used to maintain the overall type-I error due to multiple endpoints testing.

A blinded, non-comparative, sample size reassessment, based on the number of relapses occurring during the study, was conducted prior to end date of recruitment. [redacted]

[redacted]

[redacted]

## 8.1 [redacted]

[redacted]

## 8.2 [redacted]

[redacted]

## 8.3 Analysis Sets

The following data analysis sets are defined for this study:

### 8.3.1 Placebo-Controlled Period Intent-to-Treat (ITTpc) Analysis Set

The placebo-controlled Intent-to-Treat (ITTpc) analysis set will consist of all randomized subjects according to their originally assigned treatment group. The ITTpc analysis set will include all data collected during the PC period regardless if subjects early terminated treatment. The placebo-controlled Intent-to-Treat (ITTpc) analysis set will serve as the principal analysis set for efficacy assessments and inference.

### 8.3.2 Placebo-Controlled Per-Protocol (PPpc) Analysis Set

The placebo-controlled Per-Protocol (PPpc) analysis set is a subset of the ITTpc analysis set and will consist of all subjects with no major protocol violations as will be identified in the more detailed SAP developed prior to revealing of the study blind.

### 8.3.3 Placebo-Controlled Safety (STpc) Analysis Set

The placebo-controlled safety (STpc) analysis set will consist of all randomized subjects according to treatment actually administered. The STpc analysis set will include all data collected during the PC period regardless if subjects early terminated treatment.

### 8.3.4 Long-Term Safety (STLT) Analysis Set

The long-term safety ($ST_{LT}$) analysis set will consist of all randomized subjects according to treatment actually administered. The $ST_{LT}$ analysis set will include all data collected during both PC and OL periods.

## 8.4 Comparability of Study Groups at Baseline

Demographic data, baseline characteristics and MS prognostic factors for the ITTpc analysis set will be described in summary tables providing descriptive statistics broken down by treatments groups.

## 8.5 Significance Level and Multiplicity Adjustment

One (1) primary endpoint and 4 secondary end-points are pre-defined for this study. The overall significance level for this study will be 5% using two-tailed tests utilizing the hierarchical gate keeping approach to control the overall Type-I error rate. Note that all efficacy analyses described in this section refer to the PC period.

According to the gate keeping approach the primary endpoint will be tested using a two-tailed 5% significance level. If, the principal analysis of the primary endpoint statistically significantly ($p<0.05$) favors GA Depot treatment, then the 1st secondary endpoint (Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline) will be tested using a two-tailed 5% significance level. The same principle will be implemented for the 2nd, 3rd and 4th secondary endpoints according to the below listed order of testing:

| Order of Testing | End-Point to be Tested in the Order Listed |
|---|---|
| 1st | **Primary Endpoint**: Annualized Relapse Rate (ARR) |
| 2nd | **Secondary Endpoint**: Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline |
| 3rd | **Secondary Endpoint**: Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline |
| 4th | **Secondary Endpoint**: Change from baseline to Week 52 in hyperintense T2-lesion volume |
| 5th | **Secondary Endpoint**: Change from baseline to Week 52 in enhancing T1-lesion volume |

## 8.6 Efficacy Analysis

All efficacy analyses described in this section refer to the PC period. These analyses will be conducted at the time when the PC period will be completed, the PC period database is locked, and all subjects either early terminated from the study or continue treatment in the OL period.

### 8.6.1 Primary Endpoint

Annualized Relapse Rate (ARR) during the 52 weeks of the PC period as derived from the total number of confirmed relapses.

### 8.6.2 Secondary Endpoints

A total of 4 secondary endpoints are pre-defined for this study. The gate keeping approach for controlling the type-I error will be used in the following order of significance testing:

1. Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline.
2. Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline.
3. Change from baseline to Week 52 in hyperintense T2-lesion volume.
4. Change from baseline to Week 52 in enhancing T1-lesion volume.

### 8.6.3 [redacted]

[redacted]

11. [redacted]

## 8.7 Planned Method of Analysis

### 8.7.1 Principal Analysis of the Primary Endpoint

The primary endpoint of the study is the Annualized Relapse Rate (ARR) during the 52 weeks of the PC period as derived from the total number of confirmed relapses utilizing the baseline adjusted over-dispersed, exposure-weighted Poisson regression below described. Primary analysis set for inference will be the ITTpc analysis set.

[redacted]

#### 8.7.1.1 Sensitivity Analysis for the Primary Endpoint

[redacted]

- [redacted]

### 8.7.2 Secondary Endpoints Analyses

The analyses of the 4 secondary endpoints will be conducted on the ITTpc analysis set employing the gate keeping approach for controlling the type-I error in the following order of significance testing:

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

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**8.7.3.9** [redacted]

[redacted]

[redacted]

### 8.7.3.10 Proportion (%) of subjects with No Evidence of Disease Activity (NEDA-3).

NEDA-3 for an individual subject is defined as the absence of any new or enlarging T2 lesions or T1 gadolinium-enhancing lesions on any post-baseline MRI scan and no clinical relapse, and no confirmed or unconfirmed disease progression.

### 8.7.3.11 Annualized non-protocol defined relapses

Annualized non-protocol defined relapses as derived from the total number of non-protocol defined relapses including:

- Relapses with objective changes but seen >14 days from onset of symptoms.
- Relapses including only subjective sensory symptoms or other new symptoms that are regarded by the investigator as relapses but not accompanied by the protocol defined objective changes.

[redacted]

[redacted]

[redacted]

[redacted]

SAP will detail additional analyses related to quality of life outcomes.

[redacted]

[redacted]

[redacted]

[redacted]

## 8.8 Safety and Tolerability Assessments

The primary cohort for safety and tolerability inference will be the placebo-controlled safety (STpc) analysis set which will be evaluated at the end of the 52 weeks of the study PC period.

The long-term safety and tolerability will use the $ST_{LT}$ analyses set which will include all data collected during both PC and OL periods.

### 8.8.1 Adverse Events

The incidence and frequency of adverse events will be presented by System Organ Class and preferred terminology according to MedDRA dictionary. AEs will also be presented by System Organ Class, High Level Term and preferred terminology. Data will be tabulated by treatment group, gender, age and other AEs attributes. Serious adverse events and seriousness criteria will be listed and discussed on a case by case basis.

### 8.8.2 Laboratory Tests

Summary tables of measured values as well as changes from baseline as well as listings and summary tables of the clinically significant laboratory results will be generated and presented by study group.

### 8.8.3 Vital Signs

Summary tables of measured values as well as changes from baseline as well as listings and summary tables of the clinically significant vital signs results will be generated and presented by study group. Shift analysis from baseline will be provided as well.

### 8.8.4 ECG

The incidence of abnormal ECG findings will be presented by treatment group. Shift analysis from baseline will be provided as well.

### 8.8.5 Tolerability Assessments

[redacted]

## 8.9 Interim analysis

[redacted]

## 8.10 Deviations from the Statistical Plan

Deviations from the statistical plan as well as the reasons for the deviations, will be described in the clinical study report.

# 9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Access to the subject's source data and study documents will occur only with the subject's acknowledgement by signing an informed consent. The investigator will permit study-related monitoring, audits, Ethical committees and/or Institutional Review Board (IRB) reviews and regulatory inspection(s) direct access to source data and documents.

For each subject enrolled, the investigator or designee will write into the source records of the subject that the subject is enrolled in this study. The investigator is responsible for maintaining adequate case histories in the source records of each subject. Source data should be preserved for the maximum period of time permitted by local regulations and made available by the investigator in the cases described above.

# 10 QUALITY CONTROL AND QUALITY ASSURANCE

Each center will be monitored periodically to ensure compliance with the study protocol, international and local guidelines and legal aspects. Monitoring and auditing procedures defined/agreed by the Sponsor will be followed, in order to comply with ICH/GCP guidelines. This will include checking of the case report forms (CRF) for completeness and clarity, cross-checking with source documents, clarification of administrative matters and provision of additional guidance where appropriate.

# 11 ETHICS

## 11.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Documented approval from appropriate Ethics Committee(s)/Institutional Review Board(s) will be obtained for all participating centers/countries prior to study start, according to the ICH/GCP guidelines and local laws and regulations. When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained and also forwarded to the Sponsor. The Ethics Committees will be requested to supply to the Sponsor, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to ICH/GCP guidelines and applicable laws and regulations.

## 11.2 Ethical conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and investigator abide by ICH/GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the Sponsor or its representatives and/or regulatory authority representatives at any time. The investigator must agree to the inspection of study-related records by the regulatory authority/Sponsor representatives, and must allow the auditor(s) direct access to source documents and regulatory binder.

Modifications to the study protocol will not be implemented by either the Sponsor or the investigator without agreement by both parties and the Ethical Committees/IRBs. However, the investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Sponsor approval/favorable opinion. Within 5 days, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

## 11.3 Regulatory authority approvals/authorizations

Regulatory authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start.

## 11.4 Subject information and consent

A core information and informed consent form will be provided. Prior to the beginning of the study, the investigator must have the IEC/IRB written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects (e.g. subject card, questionnaire, and dairy).

Signed informed consent must be obtained before any study-specific procedure takes place. This signed informed consent form will be kept by the investigator as part of the source documents, and a copy will be provided to the study subject. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

## 11.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. pathologist report or CT scans), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws and in accordance with international guidelines where applicable. The subjects will be informed in writing (informed consent) that representatives of the Sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

# 12 DATA HANDLING AND RECORD KEEPING

Entries made into the CRF must be verifiable against source documents. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until permission given by the Sponsor for destruction.

# 13 FINANCING AND INSURANCE

All subjects participating in the study will have insurance coverage by the Sponsor, which is in line with applicable local laws and/or regulations.

# 14 PUBLICATION POLICY

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other Principal Investigators. The Principal Investigator and any investigator participating in the study, whilst free to utilize data derived from the study for scientific purposes, must discuss any publication with the Sponsor prior to release and obtain written consent of the Sponsor on the intended publication. The Sponsor recognizes the right of the Principal Investigator and any investigator participating in the study to publish the results at his/her sites upon completion of the study. However, the Principal Investigator and any investigator participating in the study must send a draft manuscript of the publication or abstract to the Sponsor 90 days in advance of submission in order to obtain written approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. The Sponsor may delay the manuscript's publication in case a patent based on the study's results needs to be filed until such patent is filed to the satisfaction of the Sponsor. In case of a difference of opinion between the Sponsor and the Principal Investigator and any investigator participating in the study, the contents of the publication will be discussed in order to find a solution which satisfies all parties involved.

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# 16 APPENDICES

## 16.1 Study flow chart and/or schedule procedure

See Table 16-1 for study procedures.

**Table 16-1a: Study procedures PC Period**

| | Screening | Treatment – PC Period | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit / Week[a],[b]** | **V1/ W (-4) Pre-treatment** | **V2/ W0 Base-line** | **V3/ W1 Phone call visit** | **V4/ W4** | **V5/ W8** | **V6/ W12** | **V7/ W16** | **V8/ W20** | **V9/ W24** | **V10/ W28** | **V11/ W32** | **V12/ W36** | **V13/ W40** | **V14/ W44** | **V15/ W48** | **V16/ W52/EoT[c]** | **Un-scheduled visit** |
| Written informed consent | X | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Physical examination | X | X | | X | | X | | | X | | | X | | | | X | X |
| Vital signs | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Laboratory tests, urinalysis | X | X | | X | | X | | | X | | | X | | | | X | |
| Serum collection | | X | | X | | X | | | X | | | X | | | | X | |
| Urine Pregnancy test (eligible women) | X | X | | | | | | | | | | | | | | X | |
| 12 lead ECG | X | | | | | | | | | | | | | | | X | |
| MRI brain scan | X | | | | | | | | X | | | | | | | X | |
| Neurological evaluations | X | X | | | | X | | | X | | | X | | | | X | X[d] |
| Administration of study drug[b] | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X[b] | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| EQ-5D-3L & TSQM-9 | | | | | | | | | | | | | | | | X | |

[a] Visits may be performed -4 +2 days from designated time points (except for screening).

[b] Study medication will be given to all subjects continuing the second year of the study at week 52

[c] A Follow up Visit should be scheduled one month after EoT visit for subjects discontinuing the study or at week 56 for those subjects electing not to continue to the OL period. For the FU visit evaluations see visit 30 /week 108 in the OL period (table 16-1b)

[d] Evaluations in an unscheduled visit will be performed as considered necessary by the investigator, except for vital signs, AEs and concomitant medication which are mandatory at each visit. For Unscheduled visits in case of a relapse/FU of a relapse, Physical and Neurological evaluations will be considered as mandatory and subjects will be re-consented.

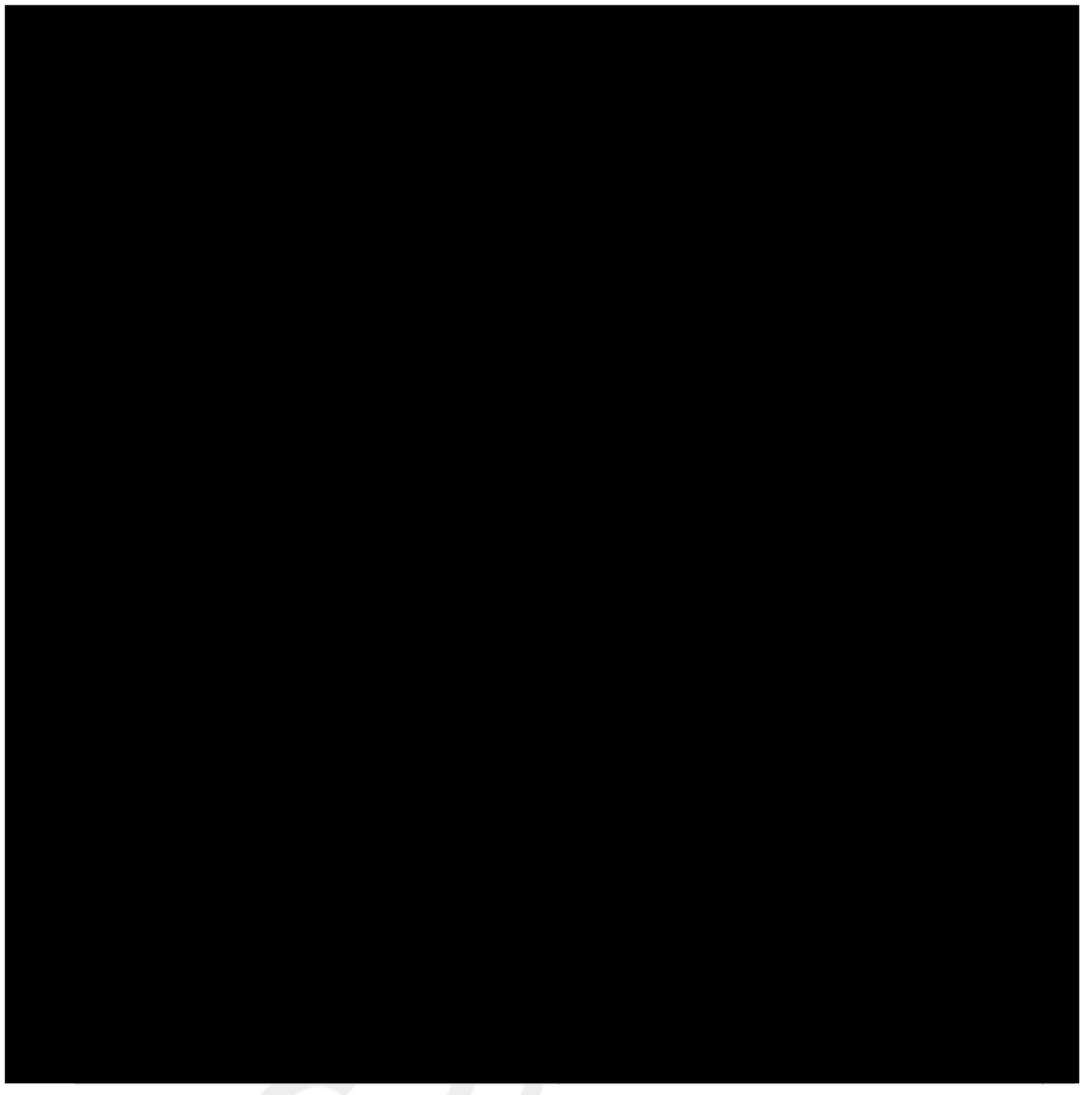
| **Table 16- 1b: Study procedures OL Period** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Treatment – OL Period** | | | | | | | | | | | | | **FU** |
| **Visit / Week[a]** | **V17/ W56** | **V18/ W60** | **V19/ W64** | **V20/ W68** | **V21/ W72** | **V22/ W76** | **V23/ W80** | **V24/ W84** | **V25/ W88** | **V26/ W92** | **V27/ W96** | **V28/ W100** | **V29/ W104 EoT** | **V30/ W108 FU** |
| Written informed consent | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | | | | | | | | | | | | | | |
| Demographic data | | | | | | | | | | | | | | |
| Medical history | | | | | | | | | | | | | | |
| Physical examination | | | X | | | X | | | X | | | | X | X |
| Neurological evaluations | | | X | | | X | | | X | | | | X | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Laboratory tests and urinalysis | | | | | | X | | | | | | | X | |
| 12 lead ECG | | | | | | | | | | | | | X | |
| MRI brain scan | | | | | | | | | | | | | X | |
| Administration of study drug | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| EQ-5D-3L & TSQM-9 | | | | | | | | | | | | | X | |
| [a] Visits may be performed -4+2 days from designated time points. | | | | | | | | | | | | | | |



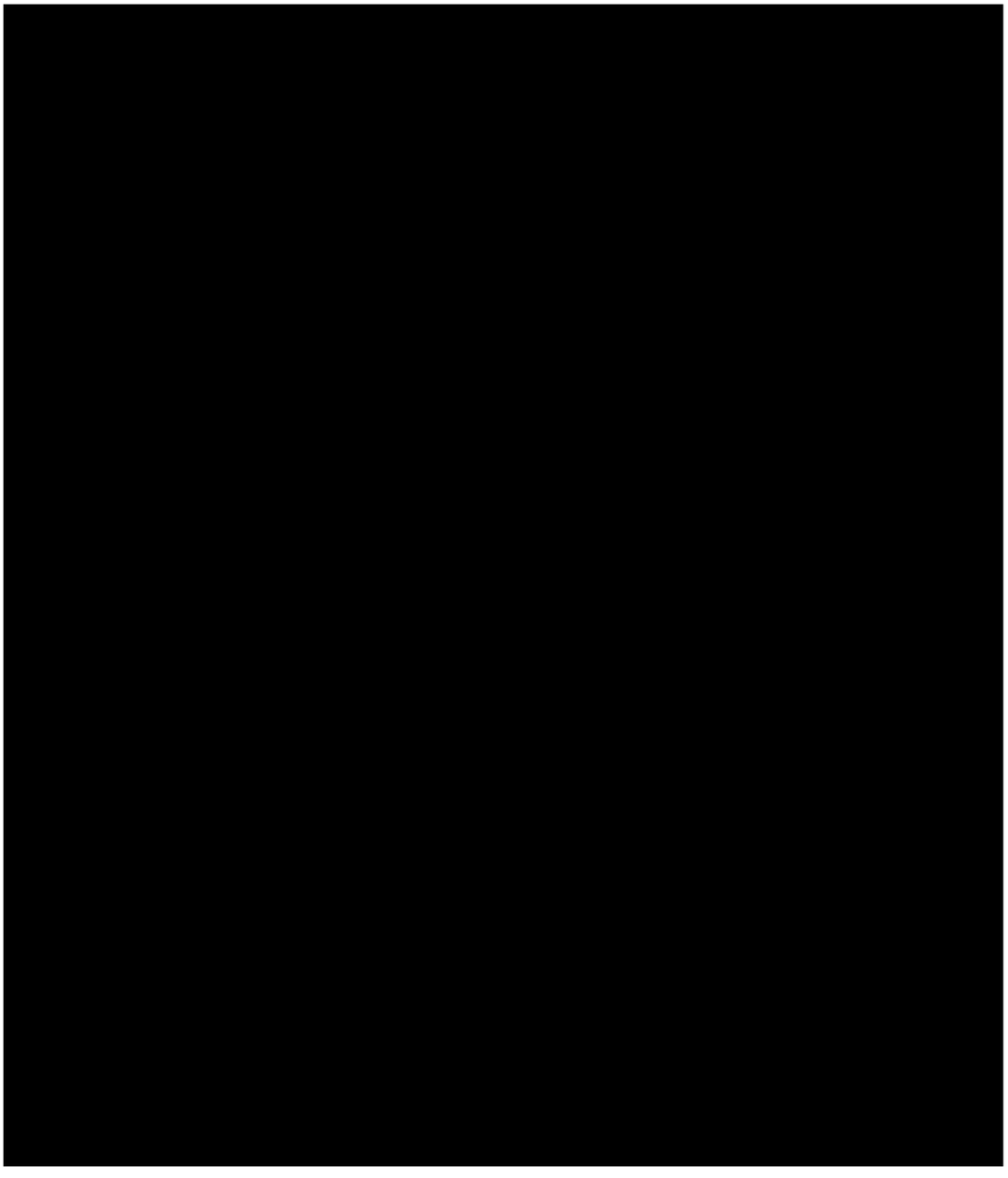
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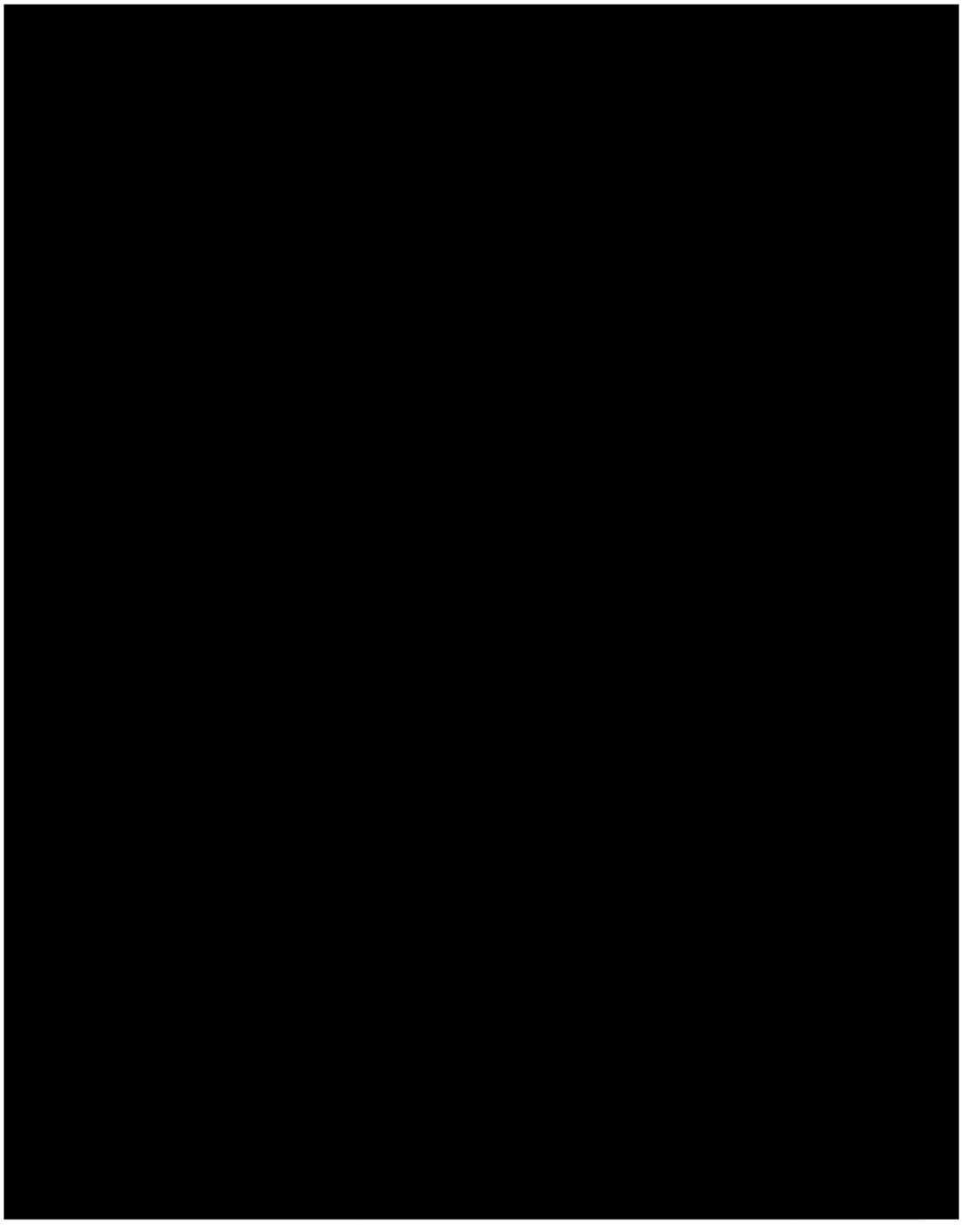
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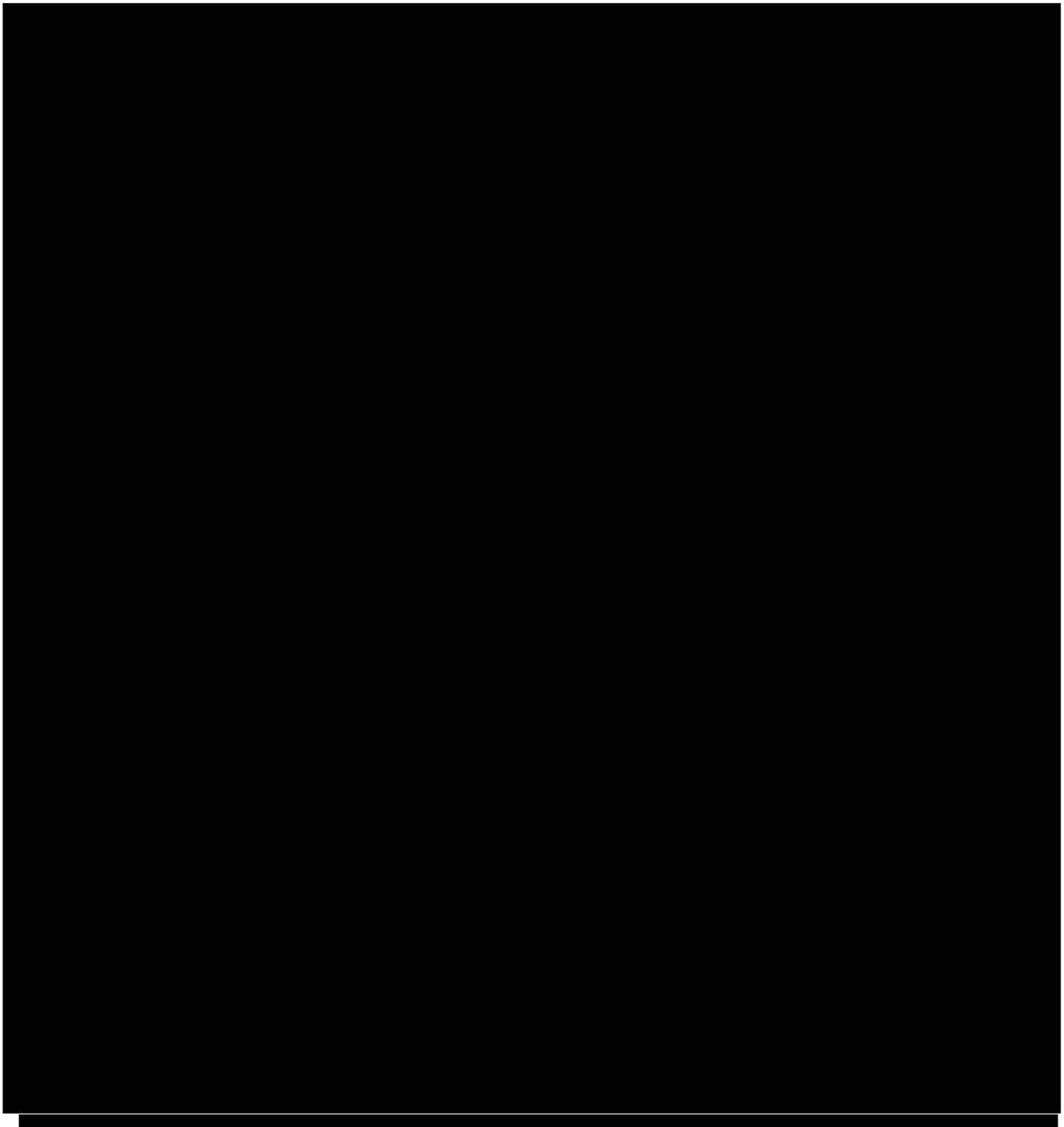






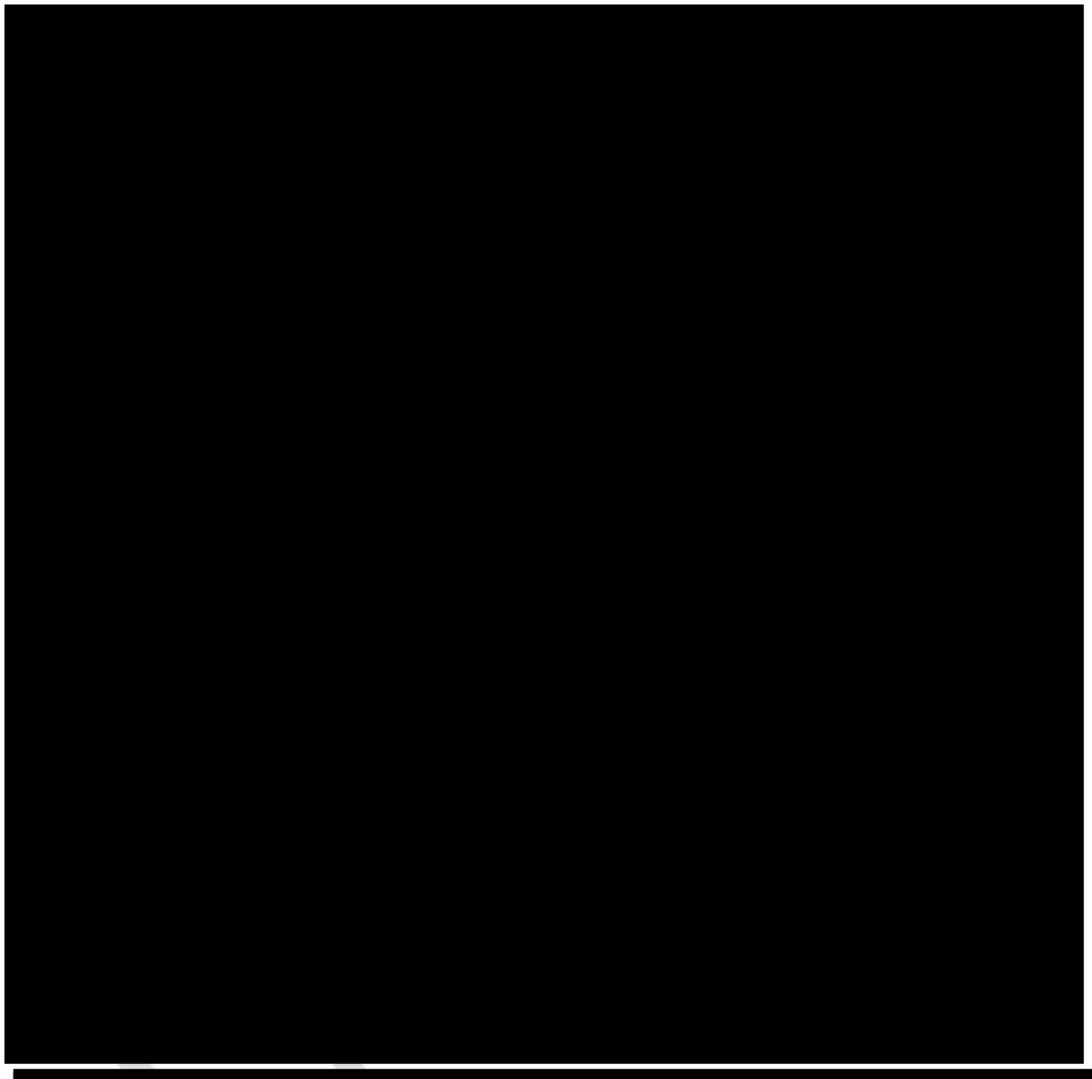














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