Statistical Analysis Plan

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

SAP with Amendment 03 approval date: 19 June 2022

Sponsor Name: Mapi Pharma, 16 Einstein St., Ness-Ziona, Israel

STATISTICAL ANALYSIS PLAN

52-Week Placebo Controlled (PC) Period

Protocol 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 Version/Date:	**Version 03 / 07 April 2021**
SAP Version/Date:	**Version 3.0 Final / June 19, 2022**
Sponsor:	**Mapi Pharma Ltd.**
SAP Author and Study Statistician:	[redacted], **Senior Biostatistician**

This document contains confidential and proprietary information and it is subjected to confidentiality protections. If you are not a designated recipient you may not review, copy or distribute this document.

Version Control

Version:	Version Date:	
[redacted]	[redacted]	[redacted]

Study No.: MI GA Depot Phase III - 001

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

Statistical Analysis Plan for:

☐ Interim Analysis

☐ Integrated Summary of Efficacy

☒ Final Analysis

☐ Integrated Summary of Safety

Version Date: Date 28-Jun-2022
(dd-Mmm-yyyy)

[redacted]

I confirm that I have reviewed this document and agree with its content.

[redacted]

TABLE OF CONTENTS

1 PREFACE 8
1.1 SCOPE 9
1.2 RESPONSIBILITIES 9
2 STUDY OBJECTIVES 10
2.1 PRIMARY OBJECTIVE 10
3 STUDY ESTIMANDS 11
3.1 PRIMARY ESTIMAND 11
3.2 SECONDARY ESTIMAND 12
4 STUDY DESIGN 13
4.1 SUBJECT SELECTION 13
4.2 DETERMINATION OF SAMPLE SIZE 16
4.3 BLINDED SAMPLE SIZE REASSESSMENT (BSSR) 16
4.4 TREATMENT ASSIGNMENT & BLINDING 17
5 STUDY CONDUCT, PROCEDURES AND EVALUATIONS 18
5.1 STUDY PROCEDURES AND EVALUATIONS 18
5.2 PROCEDURES PRIOR TO REVEALING OF THE BLIND 23
6 PLANNED ANALYSIS 28
6.1 INTERIM ANALYSIS 28
6.2 FINAL ANALYSIS 28
6.3 OPEN-LABELED WEEK-104 AND SAFETY FOLLOW-UP ANALYSES AND REPORTING 28
6.4 DATA MONITORING COMMITTEE 28
7 ENDPOINTS 29
7.1 PRIMARY EFFICACY ENDPOINT 29
7.2 INDIVIDUALIZED ANNUALIZED RELAPSE RATE 29
7.3 SECONDARY EFFICACY ENDPOINTS 29
7.4 EXPLORATORY EFFICACY ENDPOINTS 30
7.5 SAFETY OUTCOMES 34
7.6 SERUM SAMPLES FOR ANTIBODY TESTING 34
8 ANALYSIS POPULATION 35
8.1 ANALYSIS SETS 35
8.2 MAJOR PROTOCOL VIOLATIONS 36
9 GENERAL ASPECTS FOR STATISTICAL ANALYSIS 37
9.1 GENERAL METHODS 37
9.2 BASELINE DEFINITION 37

9.3 Definition Of Study Period Duration 37
9.4 Definition of Treatment Period Duration 38
9.5 Treatment Compliance 38
9.6 Significance level 38
9.7 Type I Error Control 38
9.8 Incomplete (Missing) Data 39
9.9 Software 40
9.10 Visit Windows 41
9.11 Country Geographical Region (CGR) 42
9.12 Subgroups 42

10 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 43

10.1 Subject Disposition and Withdrawals 43
10.2 Demographic and Other Baseline Characteristics 43
10.3 Medical History and Concomitant Diseases 44

11 EFFICACY 45

11.1 Primary Efficacy Analysis 45
11.2 Supportive Analyses for the Primary End Point 46
11.3 Sensitivity for the Primary Analysis 49
11.4 Secondary Efficacy Endpoints and Analyses 50
11.5 Supportive analysis for the secondary Efficacy Endpoints 53
11.6 Exploratory Efficacy Endpoint(s) Analyses 56

12 SAFETY 60

12.1 Extent of Exposure 60
12.2 Treatment Compliance 60
12.3 Tolerability 60
12.4 Adverse Events 61
12.5 Medication 63
12.6 Laboratory Evaluations 64
12.7 Vital Signs 64
12.8 ECG 65
12.9 Physical Examination 65

13 SERUM SAMPLES FOR ANTIBODY TESTING 66

14 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL 67

15 APPENDICES 68

16 REFERENCE 80

LIST OF TABLES

Table 1 : The Analysis Visit Windows 41
Table 2 - Potentially Clinically Significant (PCS) Laboratory Values 64
Table 3 - Criteria for Potentially Clinically Significant (PCS) Abnormal Vital Signs 65

LIST OF FIGURES

Figure 1: Study Design Scheme 13

LIST OF APPENDICES

Appendix 1 : Blinded Sample Size Reassessment 69

GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AR	Autoregressive
BP	Blood Pressure
CDMS	Clinical Data Management System
CO	Completers Analysis Set
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
DMP	Data Management Plan
ECG	Electrocardiogram
ET	Early Termination
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product

Abbreviation	Description
IRB	Institutional Review Board
ITT	Intent to Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LSM	Least Square Means
LDM	Lead Data Manager
LCDC	Lead Clinical Data Coordinator
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute or Minimum
mITT	Modified Intent to Treat
ML	Maximum-Likelihood
OL Period	Open Label Period
PC Period	Placebo Controlled Period
PP	Per Protocol
REML	Restricted ML
RR	Respiratory Rate
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
WHO	World Health Organization
MI	Multiple Imputation

1 PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Mapi Pharma Ltd. (Mapi) clinical trial MI GA Depot Phase III - 001 (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), and was written in accordance with SOP - Statistical Analysis Plan [redacted]. The structure and content of this SAP provides sufficient details to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Amended Clinical Study Protocol GA Depot -phase III Study protocol version 03, dated April 7 2021.
- Case report form (CRF) for GA Depot (when constructed before study initiation).
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
    - E9(R1) - Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
- ICH E3 Structure and Content of Clinical Study Reports (CSRs).
- Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, Guidance for Industry, June 2020.

This SAP describes the statistical analyses as it is foreseen before breaking the blind. The SAP will serve as a complement to the study protocol and supersedes it in case of differences between the SAP and the statistical sections of the protocol. In case of major differences, e.g. changes in the analysis related to the primary endpoint, a protocol amendment will be considered. The SAP may be updated during the study conduct and will be finalized before breaking the blind. Mapi

Pharma will assess whether data regarding COVID-19 can be analyzed as post-hoc, following the breaking of the blind.

1.1 Scope

The SAP scope is to describe the analyses planned for the 52-week Placebo Controlled Period (PC Period). A separate SAP will cover the analyses relating to the optional 52-week Open Label Period (OL Period).

1.2 Responsibilities

The Study Statistician will be responsible for the statistical analysis planning, will be responsible for the execution of all statistical programming deliverables related to Top Line Results and will have the overall accountability for the statistical programming deliverables. In addition, an unblinded statistician external to Mapi Pharma (by Mapi Pharma's CRO), will be responsible for providing ongoing unblinded data to the Data Monitoring Committee.

2 STUDY OBJECTIVES

2.1 Primary Objective

This multinational, multicenter, randomized, double blind, placebo-controlled study is designed to assess the efficacy, safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administrated once every four weeks, as compared to placebo in a study design of 52 weeks' duration.

3 STUDY ESTIMANDS

3.1 Primary Estimand

3.1.1 Estimand Elements:

The primary estimand construction elements for this study are:

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

3.1.2 ICE's Components Definitions

[redacted]

[redacted]

3.2 Secondary Estimand

3.2.1 Estimand Elements:

The following are the study Secondary Estimand construction elements to be tested as main supportive analysis:

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

The secondary estimand will be based on effectiveness (de-facto) assumption (‘estimand 6’ and [redacted]

4 STUDY DESIGN

This study is a multinational, multicenter, randomized, Phase-III, double blind, parallel group, placebo-controlled study designed to assess the efficacy, safety and tolerability of GA Depot, a long-acting IM injection of glatiramer acetate, administered once every four weeks in subjects with Relapsing forms of Multiple Sclerosis. A total of [redacted] Eligible subjects will be randomly allocated to either treatment with GA Depot, or to treatment with matching placebo using a 1:1 randomization scheme of [redacted] Following the conduct of the pre-planned blinded, non-comparative, sample size reassessment the study size was increased to [redacted] (see section 4.3).

Following screening and randomization, the study will be comprised of two treatment periods:

- In the placebo-controlled period (PC period), during the first 52 weeks of the study immediately following randomization, subjects will receive either 40 mg of GA Depot IM or matching placebo, once every 4 weeks for a total of [redacted].
- Subjects who complete the PC period of the study will be permitted to continue into the open label period (OL period) for an additional 52 weeks, in which all patients will receive 40 mg of GA Depot IM once every 4 weeks for a total of [redacted].

[redacted]

4.1 Subject Selection

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

4.1.1 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. Subject 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 the McDonald Criteria.
5. Subjects should be ambulatory with 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 and from screening visit to baseline visit.
7. No systemic corticosteroid treatment or ACTH within one month before screening visit.
8. Subjects that experienced at least one of the following:
    10. At least one documented relapse in the 12 months prior to screening, or
    11. At least two documented relapses in the 24 months prior to screening, or
    12. One documented relapse between 12 and 24 months prior to screening with at least one documented T1-Gd enhancing lesion in MRI performed 0-12 months before screening.
9. Women capable of childbearing must have a negative urine pregnancy test at screening and baseline visit and use an adequate contraceptive method throughout the study.

4.1.2 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, 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/mm3 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 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.

4.2 Determination of Sample Size

The sample size calculation was aimed to power the study for the primary estimand using the associated estimator as specified in sections 11.1. The sample size and power were estimated based on simulation study designed according to the following assumptions:

- [redacted]

[redacted]

4.3 Blinded Sample Size Reassessment (BSSR)

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. The timing of assessment and the methodology to be employed was determined while treatment allocation is unrevealed, and study was still enrolling. [redacted]

[redacted]
suggested that the study size was to be increased to [redacted] via protocol amendment for maintaining the original study power on [redacted] (see final report in **Appendix 1: Blinded Sample Size Reassessment**), taking into account a typical overrun, the final sample size was determined at 1,016 randomized subjects.

4.4 Treatment Assignment & Blinding

Clinical Research Organization (CRO) personnel, independent of the study team, will prepare the randomization list using [redacted]. An independent statistician (not involved in the study) will review the code prior to any treatment assignment. [redacted]

Subjects will be randomized in a 1:1 ratio to one of the following treatment groups:

- GA Depot
- Placebo for GA Depot

Subjects who are withdrawn from the study and/or study treatment during the Placebo Controlled period will not be replaced.

The patients, the investigators, the Sponsor and all personnel involved in subjects' assessment, monitoring, the assigned Study Statistician [redacted] and data management team are blinded to the subject treatment assignment. However, due to the requirements to report Serious Unexpected Suspected Adverse Reactions (SUSARs), there are specific unblinded staff at the CRO within the safety team who will have access to the treatment code via the IWRS.

[redacted]

5 STUDY CONDUCT, PROCEDURES AND EVALUATIONS

5.1 Study Procedures and Evaluations

- **Demographic data and medical history:** This information will be collected at screening to ensure suitability according to the inclusion and exclusion criteria.
- **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 at baseline, and [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, [redacted]
- **12-lead ECG**: The ECG will be recorded at [redacted]
- **MRI brain scan:** MRI scans will be conducted at screening, 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 screening [redacted]

- **Laboratory investigations:** Clinical laboratory testing will be performed 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.

Table 1: Placebo Controlled (PC) Period Procedures

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.
[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.

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.

5.1.1 Stopping rules/discontinuation criteria 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.

5.2 Procedures Prior To Revealing of the Blind

The Author of this SAP as well as all personnel approving this SAP are currently fully blinded to the randomization scheme.

[redacted]

[redacted]:

5.2.1 "Clean" Study Database

The study database will be considered to be "clean" when **all** of the below required tasks have been completed:

1. [redacted]

5.2.2 Disallowed Pre-Study Medications

Use of the following treatments is NOT allowed prior to study entry:

- Use of experimental / investigational drug, and / or participation in other clinical studies within 6 months prior to GA Depot administration.
- Any off-label drug use for MS treatment such as high dose simvastatin and biotin within 6 months prior to screening.
- Use of immunosuppressant (including Mitoxantrone [Novantrone®]), Alemtuzumab, cladribine or cytotoxic agents within 5 years prior to the screening visit.
- Previous use of either natalizumab (Tysabri®) or any anti-B cell agent within 9 months prior to screening.
- 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/mm3 at screening.
- Previous treatment with immunomodulators (including IFNIβ 1a and 1b, and IV Immunoglobulin (IVIg) within 2 months prior to screening.
- Previous use of GA or any other glatiramoid.
- Previous use of Teriflunomide within 12 months if no accelerated elimination procedure was used.
- Chronic (more than 30 consecutive days) systemic (IV, PO or IM) corticosteroid treatment within 6 months prior to screening visit.
- Previous total body irradiation or total lymphoid irradiation.
- Previous stem-cell treatment, autologous bone marrow transplantation or allogeneic bone marrow transplantation.
- Subjects receiving treatment with anticoagulants.

5.2.3 Disallowed Concomitant Medications

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

- Systemic corticosteroids except for the treatment of acute MS exacerbations, if considered appropriate by the Investigator.
- ACTH.
- Any immuno-modulating treatment (e.g. interferon beta, natalizumab or other monoclonal

antibody therapy).

- 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.

5.2.4 Database freezing Procedures

5.2.4.1 [redacted]

[redacted]

5.2.5 [redacted]

[redacted]

5.2.6 Database Unblinding Activities by the CRO

[redacted]

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

5.2.7 QC of Randomization Scheme

Following the receipt of the SDTM but prior to initiation of any statistical analyses as per this SAP, unblinding will be performed and the appropriateness of treatment assignment will be verified.

6 PLANNED ANALYSIS

6.1 Interim Analysis

[redacted]

6.2 Final Analysis

All final, planned analyses identified in this SAP will be performed only after the last subject has completed the PC Period. The randomization codes will not be unblinded until SAP has been approved and all items defined in 'Procedure Prior to Revealing of the Blind' has been executed.

6.3 Open-Labeled Week-104 and safety follow-up Analyses and Reporting

[redacted]

6.4 Data Monitoring Committee

A DMC [redacted] will meet periodicall [redacted] Data will be provided to the DMC members by an unblinded statistician external to Mapi Pharma. The DMC will provide recommendations on study continuation or early discontinuation in case there is a concern regarding safety. The specific responsibilities and the composition of the committee are outlined in a separate document, the DMC Charter, which will also include details of the outputs provided for the committee's meetings.

7 ENDPOINTS

7.1 Primary Efficacy 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.

The number of protocol defined relapses during the 52 weeks of the PC Period will be summed per subject and will be used for the primary analysis. The number of protocol defined relapses will be adjusted to the Exposure to Study Duration. Exposure to study duration will be calculated [redacted]

7.2 [redacted]

[redacted]

7.3 Secondary Efficacy Endpoints

The following are the secondary endpoints presented in hierarchical order for the gatekeeping approach (hierarchical fixed sequence) to preserve type I error:

7.3.1 1st Secondary endpoint: Cumulative Number of new Enhancing Lesions on T1-Weighted Images

[redacted]

- [redacted]

7.3.2 2nd Secondary endpoint: Cumulative Number of New or Newly Enlarging hyperintense T2 Lesions at Week 52 as compared to baseline

[redacted]

Before implementing the above, scans at early termination visit will be classified to the closest schedule visit.

7.3.3 3rd Secondary endpoint: Change from Baseline to Week 52 in hyperintense T2 Lesion Volume

[redacted]

7.3.4 4th Secondary endpoint: Change from baseline to Week 52 in enhancing T1-lesion volume

[redacted]

7.4 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be evaluated to provide additional insight into the therapeutic effect of GA Depot without any control for Type I error and thus p-values will be provided nominally without adjustment. Analysis will display comparisons between GA Depot and placebo at all available visits.

The exploratory endpoints to be analyzed are:

7.4.1 [redacted]

7.4.2 [redacted]

7.4.3 [redacted]

7.4.4 [redacted]

7.4.5 [redacted]

7.4.6 [redacted]

7.4.7 [redacted]

7.4.8 [redacted]

7.4.9 [redacted]

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

[redacted]

E_t [redacted]

E_0 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

t [redacted]

[redacted]

[redacted]

[redacted]

7.4.10 [redacted]

[redacted]

7.4.11 [redacted]

[redacted]

- [redacted]
- [redacted]

7.5 [redacted]

[redacted]

7.6 [redacted]

[redacted]

8 ANALYSIS POPULATION

8.1 Analysis Sets

The efficacy endpoints will utilize the data collected only during the PC Period of the study.

The following analysis sets will be used:

8.1.1 Placebo Controlled Period Intention-to-Treat Analysis Set (ITTpc set):

In accordance with the intention-to-treat principle, all randomized subjects will be included in this analysis set. The subjects will be grouped according to the treatment to which they were originally assigned to (planned randomization). The Intention-to-Treat (ITTpc) analysis set will serve as the principal analysis set for efficacy assessments and inference where applicable.

8.1.2 Placebo Controlled Period Safety Analysis Set (STpc set):

The Safety analysis set will include all randomized subjects who took at least one dose of the study drug. The subjects will be grouped according to the treatment actually received. The STpc analysis set will serve to compare safety and tolerability data between the 2 randomized groups.

8.1.3 MRI Placebo Controlled Period Analysis Set (MRIpc set):

The MRI analysis set (MRIpc set) will consist of all randomized subjects who had a least one post-baseline valid MRI scan during the 52 weeks of the PC Period. The subjects will be grouped according to the treatment to which they were originally assigned to (planned randomization). The MRIpc set will serve to compare MRI data between the 2 randomized groups.

8.1.4 Placebo Controlled Period Modified Intention-to-Treat Analysis Set (mITTpc set):

The mITTpc analysis set will include all randomized participants who took at least one dose of the study drug and have at least one post-baseline efficacy assessment. The efficacy assessments for which this set is defined will include: EDSS and MSFC. The subjects will be grouped according to the treatment to which they were originally assigned to (planned randomization).

8.1.5 Placebo Controlled Period Per Protocol Analysis Set (PPpc set):

The Per-Protocol analysis set (PPpc set) will consist of all randomized subjects without any major protocol violations (see: definition in section 8.2). The subjects will be grouped according to the treatment to which they were originally assigned to (planned randomization).

8.2 Major Protocol Violations

[redacted]

Following the receipt of the blinded freeze database, a list with subjects to be excluded from the Per-Protocol (PPpc) analysis set will be determined by [redacted]. This process will be documented in a Blinded Data Review Meeting minutes and prior to the receipt of the freezed unblinded database.

In case other deviations detected during the study period are considered to potentially influence the evaluation of the primary efficacy endpoint, these deviations will be documented prior to the database freeze during blinded data review meeting and the subjects having these deviations will be excluded from the PP Set.

9 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

9.1 General Methods

All data from all subjects randomized into the study will be included in subject data listings. The listings will be sorted by treatment group, center and subject number (and by visit, if applicable).

9.2 Baseline Definition

Any measurement recorded in the database as taken prior to the study first dose is classified as **pre-dosing observations** while those taken on the day or after the day of first study dose are considered as **on-treatment observations.** The last data recorded prior to first study drug administration will be considered as baseline data. Generally, these are the data recorded at Visit 2 (baseline visit). If these data are missing, then the last data recorded prior to that visit will be used.

9.3 Definition Of Study Period Duration

Study period duration calculated for each subject, given in days, will be calculated a

9.4 Definition of Treatment Period Duration

Treatment period duration (Exposure STpc) for each subject [redacted]

9.5 Treatment Compliance

Percent (%) of study IP drug compliance will be [redacted]

9.6 Significance level

Significance testing will be 2-sided using $\alpha = 0.05$, unless otherwise specified. For the analysis of the primary and secondary efficacy endpoints, a study-wise overall significance level of 0.05 will be maintained.

9.7 Type I Error Control

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 (fixed sequence) approach to control the overall Type-I error rate. According to this approach the primary endpoint will be tested using a two-tailed 5% significance level. If, the principal analysis of the primary endpoint is found statistically significant ($p<0.05$) favors GA Depot treatment, then the 1st secondary endpoint (Cumulative Number of Enhancing Lesions on T1-Weighted Images) will be tested using a two-tailed 5% significance level. Type-I error will be further controlled for the 2nd, 3rd and 4th secondary endpoints by testing the next secondary endpoint only in case the preceding endpoint will have a p-value less or equal to 0.05 according to the order specified in Section 7.3 and the following table

Hierarchy	End - Point
Primary	**Primary Endpoint**: Annualized Relapse Rate (ARR)
1st	**Secondary Endpoint:** Cumulative Number of new Enhancing Lesions on T1-Weighted Images
2nd	**Secondary Endpoint:** Cumulative Number of New or Newly Enlarging T2 hyperintense Lesions as compared to baselined
3rd	**Secondary Endpoint**: Change from Baseline to Week 52 in T2 hyperintense Lesions Volume
4th	**Secondary Endpoint**: Change from Baseline to Week 52 in T1 Enhancing Lesions Volume

9.8 Incomplete (Missing) Data

[redacted]

9.8.1 Mechanism of missing Data

Early terminations will be classified according to the following three types of missing values which [redacted]

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

[redacted]

9.8.2 Tipping Point of missing longitudinal data

To explore the possible impact of missing relapse data on the primary analysis results [redacted] ivity analysis using [redacted] will be , .(performed (see section 11.3.1

9.8.3 Handling of missing longitudinal data

[redacted]

- [redacted]
- [redacted]

Safety data will not be subject to any imputation and will be summarized on an observed case basis.

9.8.4 Incomplete Date Imputation

In some cases, the database reported dates were partial. That is, either the day, the month or both were missing. In such a case and if not stated otherwise, full date will be imputed as follows:

- If the day was missing it will be imputed as the first day of the month
- If month was missing it will be imputed as January of that year

9.9 Software

All statistical analyses and summaries will be produced using SAS [redacted]

9.10 Visit Windows

The acceptable visit dates windows of observation are specified as in Table 1 : **The Analysis Visit Windows**. Data obtained within the acceptable windows will be used for analysis or presentation. If the dates of observation are out of the following acceptable range, data obtained on those days will not be used for analysis or summary statistics. However, all data as captured will be listed.

Unless otherwise specified, baseline is defined to be the last observed value of the parameter of interest prior to first study drug administration. Typically, this will occur at the baseline visit (V2). For other visits, if there are multiple data in a window, the closest data to the nominal day will be used. If the distance to the nominal day is the same, the data of later date will be used.

In case assessments are done at the Early Termination visit, these assessments will be used as data for the scheduled visit closest to the early termination time point, in case the corresponding data are missing from this visit.

Table 1 : The Analysis Visit Windows

Analysis visit	Nominal Day	Window
[redacted]		

9.11 Country Geographical Region (CGR)

[redacted]

9.12 Subgroups

At least the following subgroup analyses have been pre-planned. The subgroup analyses will be performed at least for the primary endpoint and for adverse events. Selected baseline data will be presented for the subgroups as well.

- [redacted]

10 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

10.1 Subject Disposition and Withdrawals

Subjects disposition will be summarized as follows and presented for each treatment group, and overall, when applicable. The percentages will be calculated based on the number of randomized subjects, unless otherwise specified.

- [redacted]
  - [redacted]

[redacted] in the ITT Set)

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

10.2 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the ITT, and Safety sets, by treatment group and overall.

- [redacted]

- If age will be missing it will be calculated as the difference in days between the date of birth and date of screening and converted to years [redacted]
- Gender will be broken down for Male and Female with child bearing potential (Y/N).

- MS History:
  - Time from onset of MS symptoms, Time since Date of RMS diagnosis and Time since date of most recent MS relapse will be summarized as continuous variables.
    - [redacted]

[redacted]

10.3 Medical History and Concomitant Diseases

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The medical history data will be summarized with frequencies and percentages of subjects with at least one medical history item, and subjects frequencies and percentages on the System Organ Class (SOC) and Preferred Term (PT) levels. The number of events will also be summarized. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. The summary of medical history data will be done for the Safety set broken down by treatment group.

11 EFFICACY

11.1 Primary Efficacy Analysis

The primary endpoint of the study is the Annualized Relapse Rate (ARR) during the 52 weeks of the PC Period as derived from the exposure-weighted total number of confirmed relapses (section 7.1).[redacted] Primary analysis set for inference will be the ITT set as above noted. Only data collected under PC Period will be included.

[redacted]

[redacted]

11.1.1 Data Preparation

[redacted]

11.1.2 Primary Analysis Model (Primary Estimator)

Analysis of the primary endpoint (NRELAPSE) will be based on the GA Depot vs. placebo contrast

[redacted]

The SAS® code planned for the analysis is outlined below:

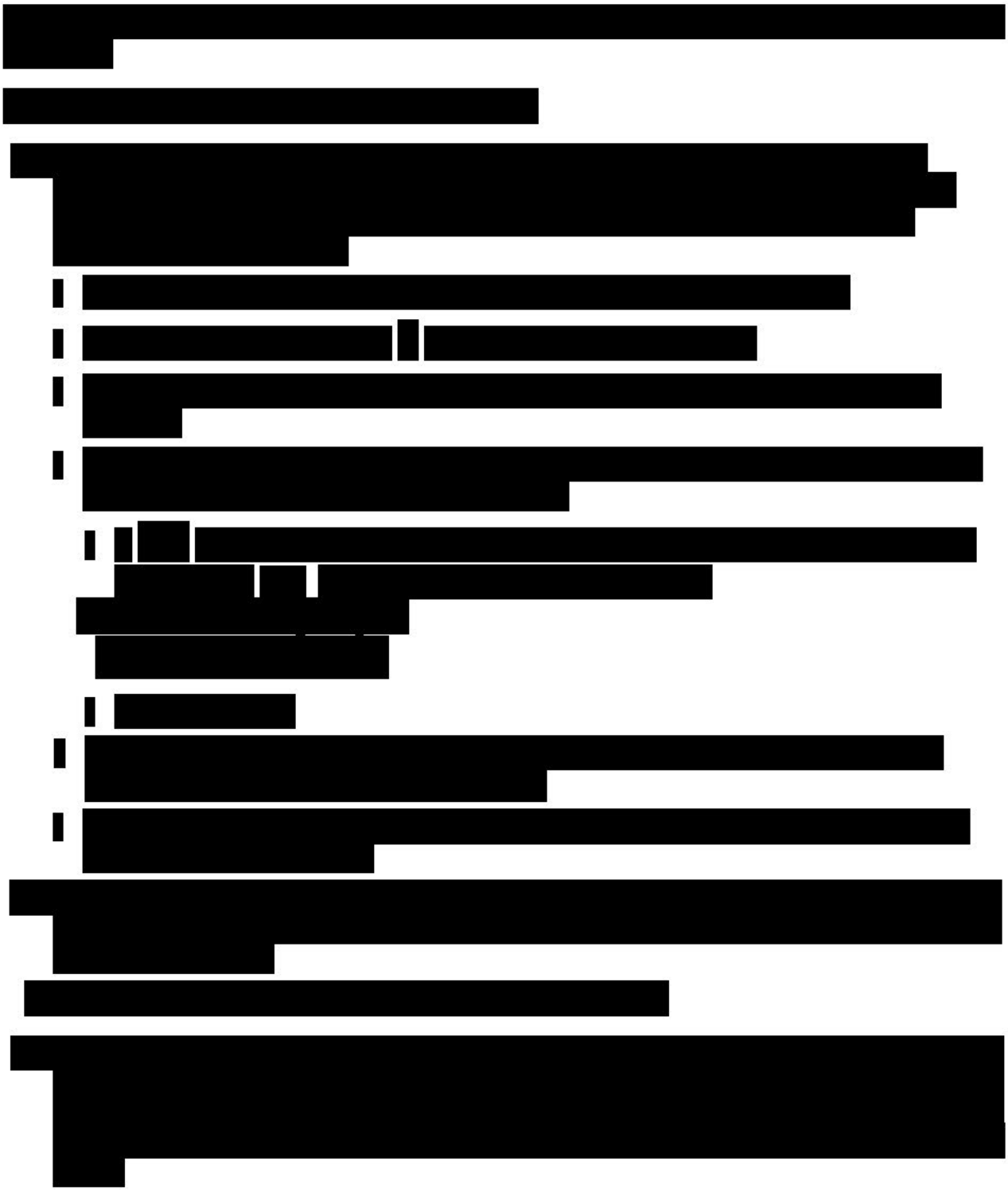
[redacted]

11.2 Supportive Analyses for the Primary End Point

The following analyses will be supportive to the primary analysis

11.2.1 [redacted]

[redacted]



[redacted]

11.2.2 Supportive Analysis Using Different Analyses Sets

The primary analysis described above will be repeated for the mITT and PP Analysis Sets

11.2.3 Supportive Analysis Using an Analysis of Covariance for the IARR

[redacted]

11.2.4 Subgroup Analysis

Subgroup analyses will be performed for factors defined in section 9.12 of this document. Each subgroup will be analyzed separately for the primary endpoint using same model similar to the primary analysis described in section 11.1.211.2.3 including additional fixed factors for the subgroup variable and interaction term between the treatment group, and subgroup variable.

[redacted]

11.3 Sensitivity for the Primary Analysis

The robustness of the primary analysis will be explored employing the following

11.3.1 [redacted]

[redacted]

11.3.2 Sensitivity Analysis Using Additional Baseline Covariates

The primary analysis described in section 11.1 will be repeated for the ITT Analysis Set introducing additional baseline covariates:

Baseline prognostic factors and demographics found to be nominally different ($p<0.05$) between study groups at baseline:

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

11.3.3 Sensitivity Analysis Using Over-Dispersed Poisson Regression

The primary analysis model described in section 11.1 will be repeated for the ITT Analysis Set replacing the Negative Binomial assumption with the Over-Dispersed Poisson Regression (SAS® PROC GENMOD). The same covariates and offset variable employed in the primary analysis model will be used in this baseline adjusted Over-Dispersed Poisson Regression while [redacted]

11.3.4 [redacted]

[redacted]

11.4 Secondary Efficacy Endpoints and Analyses

All analyses of secondary efficacy endpoints will be performed using the MRI analysis set (MRIpc). According to the hierarchical methods specified in section 9.7 and according to the following order, each secondary endpoint will be inferentially tested provided that the preceding endpoint was statistically significant.

11.4.1 1st Secondary Endpoint: Cumulative Number of new Enhancing Lesions on T1-Weighted Images

The cumulative number of new enhancing lesions during the 52 weeks of the PC Period will be calculated per subject as the sum of lesions observed at week 24 and at week 52 pre-planned scans.

[redacted]

[redacted]

11.4.2 2nd Secondary Endpoint: Cumulative number of new or newly enlarging hyperintense T2 lesions at Week 52 as compared to baseline

The cumulative number of new or newly enlarging T2 lesions during the 52 weeks of the PC period will be performed on the MRI analysis set and will be derived based on [redacted]

11.4.3 3rd Secondary Endpoint: Change from baseline to Week 52 in hyperintense T2-Lesion Volume

The change from baseline to weeks 24 and 52 in hyperintense T2 Lesion Volume will be calculated for each subject. Missing data will not be imputed on subject level for this secondary endpoint. However, the analysis of change from baseline to week 52 will use the likelihood-based [redacted]

[redacted]

11.4.4 4th Secondary Endpoint: Change from baseline to Week 52 in enhancing T1-lesion volume

The change from baseline to weeks 24 and 52 in enhancing T1 Lesion Volume will be calculated for each subject. Missing data will not be imputed on subject level for this secondary endpoint. The likelihood-based approach using MMRM will be used similarly as described above for the Change from baseline in hyperintense T2- lesion volume above (see 11.4.3) replacing Hyperintense T2-lesions volume at baseline with enhancing T1 Lesion Volume at baseline as [redacted]

[redacted]

11.5 [redacted]

11.5.1 [redacted]

[redacted]

11.5.2 [redacted]

[redacted]

11.5.2.1 Data Preparation and Imputation Procedure

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

The following example SAS code will be used.

[redacted]

11.6 [redacted]

[redacted]

11.6.1 [redacted]

11.6.2 [redacted]

11.6.3 [redacted]

11.6.4 [redacted]

11.6.5 [redacted]

11.6.6 [redacted]

[redacted]

11.6.7 [redacted]

[redacted]

11.6.8 [redacted]

[redacted]

11.6.9 [redacted]

[redacted]

11.6.10 [redacted]

[redacted]

11.6.11 [redacted]

[redacted]

11.6.12 [redacted]

[redacted]

12 SAFETY

All safety assessments will use the Safety Analysis Set (STpc) which will include all randomized subjects who took at least one dose of the study drug according to the treatment actually received. The STpc analysis set will serve as the principal analysis set for safety and tolerability analyses.

12.1 Extent of Exposure

Exposure to study Drug for safety supposes will be calculated as (see general definition in section9.4):

[redacted]

The following information will be summarized by treatment group and overall.

- The number of subjects exposed to study treatment
- Mean Duration of exposure (days)
- Total exposure to study treatment, expressed as person years (sum of exposure to study treatment)

12.2 Treatment Compliance

The proportion of used medication out of scheduled medication will be calculated based on the actual monthly administered dose of study drug (see general definition in 9.5) and summarized by treatment group with descriptive statistics.

12.3 Tolerability

Tolerability will be assessed using the frequency, incidence and severity of post injection site reactions (ISRs) as well as for immediate post injection systemic reactions (IPIRs). The proportion of subjects who early discontinued from randomized treatment due to any reason and due to AEs and the time (days) from randomization to discontinuation will be summarized and illustrated with Kaplan-Meier curves by treatment group. [redacted]

12.4 Adverse Events

Adverse events will be recorded from the time when a subject has signed the Informed Consent Form till the follow-up visit. Adverse events will be coded using the latest MedDRA version and analyzed for the safety set. Adverse events will be presented by SOC and PT and summarized by treatment group. Only treatment emergent adverse events (TEAEs) will be summarized. TEAEs are defined as all AEs that start on or after the start of first study drug administration during the PC Period or AEs that worsen during this period (or within 4 weeks after last study treatment). The summary tables will be presented by treatment group, displaying the frequency and percentage of total subjects, the number of events and events adjusted to exposure by SOC and PT. Sorting will be performed using the internationally agreed order for MedDRA SOC sorting.

The derived dictionary used in the analyses displaying the MedDRA System Organ Class (SOC), the Preferred Term (PT) and the AE Verbatim Term as specified by the Investigator, will be provided.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA PT) more than once will only be counted once for that event in the number of subjects but all occurrences of the same event will be counted in the number of events.

Events with a missing start time, but with a start date equal to the date of first dose of study drug will be considered treatment-emergent. If the AE start date is incomplete, it will be imputed as follows for the purpose of determining TEAE:

- If the start date is completely missing, the start date will be equal to the date of the first dose of study treatment. However, if the stop date is not missing and is before the date of the first dose of study treatment, then the stop date will be used instead.
- If the start day is missing, but the month and year are not missing and are equal to the month and year of the first study dose during the PC period, then this event will be considered as TEAE.
- If the start day and month are missing, then the first day of the first month (January) will be used.

The original date and time will be shown on all listings of AEs. Listings will be provided for all AEs, serious AEs, AEs leading to study treatment discontinuation, AEs leading to deaths.

The following summaries will be provided:

- [redacted]

12.4.1 Most Common TEAE's

The following analyses will be performed for the most common TEAEs (at least 5% reported PTs in any treatment group):

- [redacted]

12.5 Medication

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD, version 2019Mar01 Global B3). Medications with a stop date before the first date of study drug dosing will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing or ongoing at PC Period completion will be considered concomitant medications. The prior and concomitant medications will be summarized separately.

Other prior and concomitant medications will be presented in tabular form using the ATC Level [redacted]

If the medication start date is incomplete, then it will be imputed as follows for the purpose of determining concomitant use:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If the medication stop date is partial, then it will be imputed as follows for the purpose of determining concomitant use:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

The summary of prior and concomitant medications will be done for the Safety set broken down by treatment group.

12.6 Laboratory Evaluations

Laboratory data are to be collected at [redacted]

Please note that all laboratory data analyses will make use only of lab data obtained from the study central laboratory [redacted]. Other tests performed by the local sites laboratories [redacted]

Analyses of safety laboratory data will be performed in the following manner:

- [redacted]

Parameter	Sex	High
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

* ULN – Upper Limit of age-sex matched normal range

12.7 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 screening, and at all visits. BP (systolic and diastolic) will be measured throughout the study using the same arm, by means of a BP measuring device. The 2 repeated measurements performed one after the other with up to 15 minutes interval between the two measurements will be recorded in the CRF and will be averaged for the purpose of analysis.

Vital signs at each treatment visit will be analyzed in the following manner:

- [redacted]

[redacted]

[redacted]

[redacted]

12.8 ECG

The [redacted] will classify each ECG as either "normal", "abnormal not clinically significant (NCS)", or "abnormal clinically significant (CS)". [redacted]

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

12.9 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 at baseline and at [redacted]

Abnormal physical examination findings will be listed and summarized by visit and treatment group. The abnormal values will be further classified as clinically significant and not clinically significant based on the investigator's interpretation. In addition to the summary, all abnormal findings classified as clinically significant will be listed.

13 [redacted]

[redacted]

14 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

1) [redacted]

15 [redacted]

[redacted]

[redacted]

[redacted]



















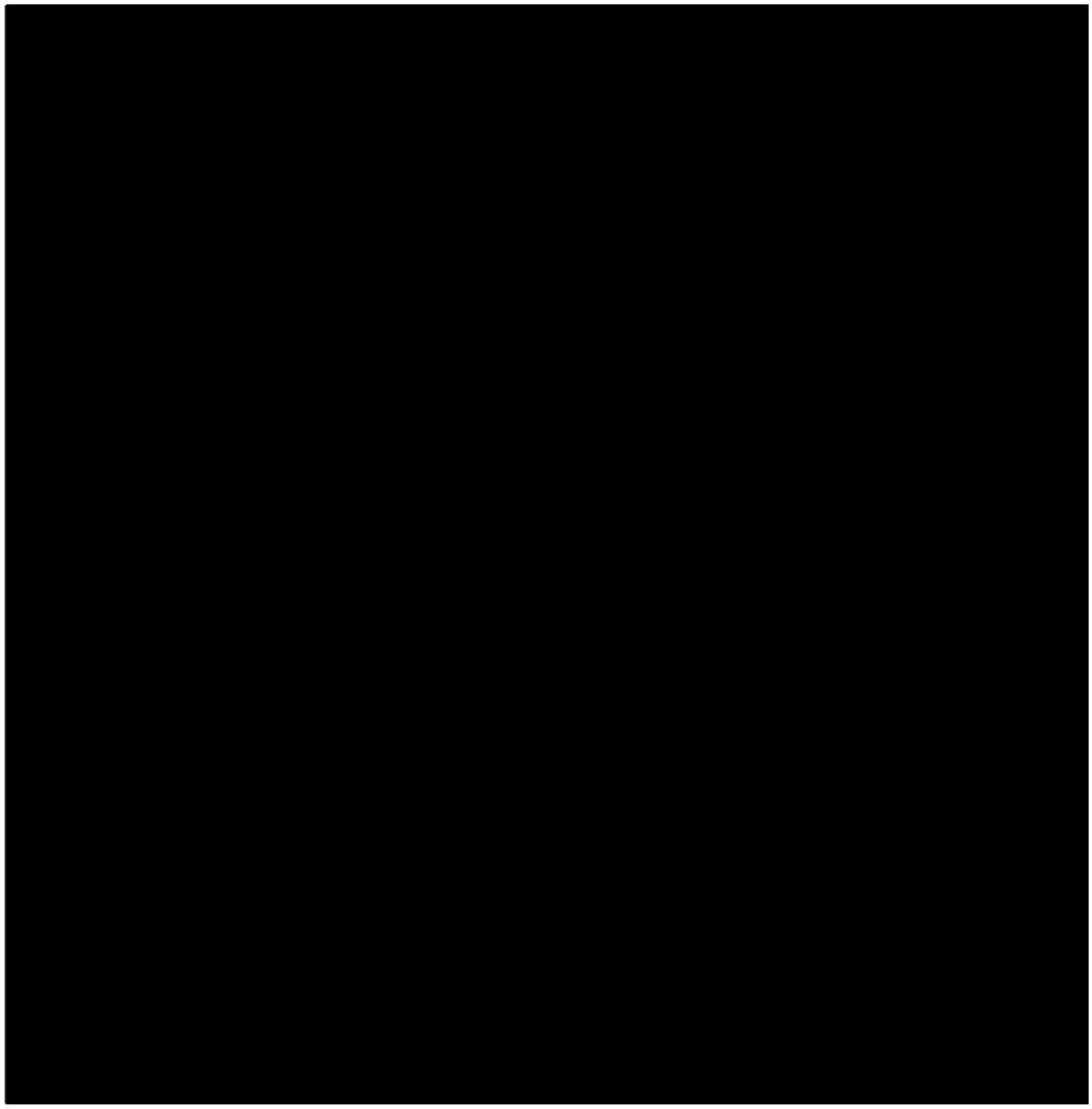






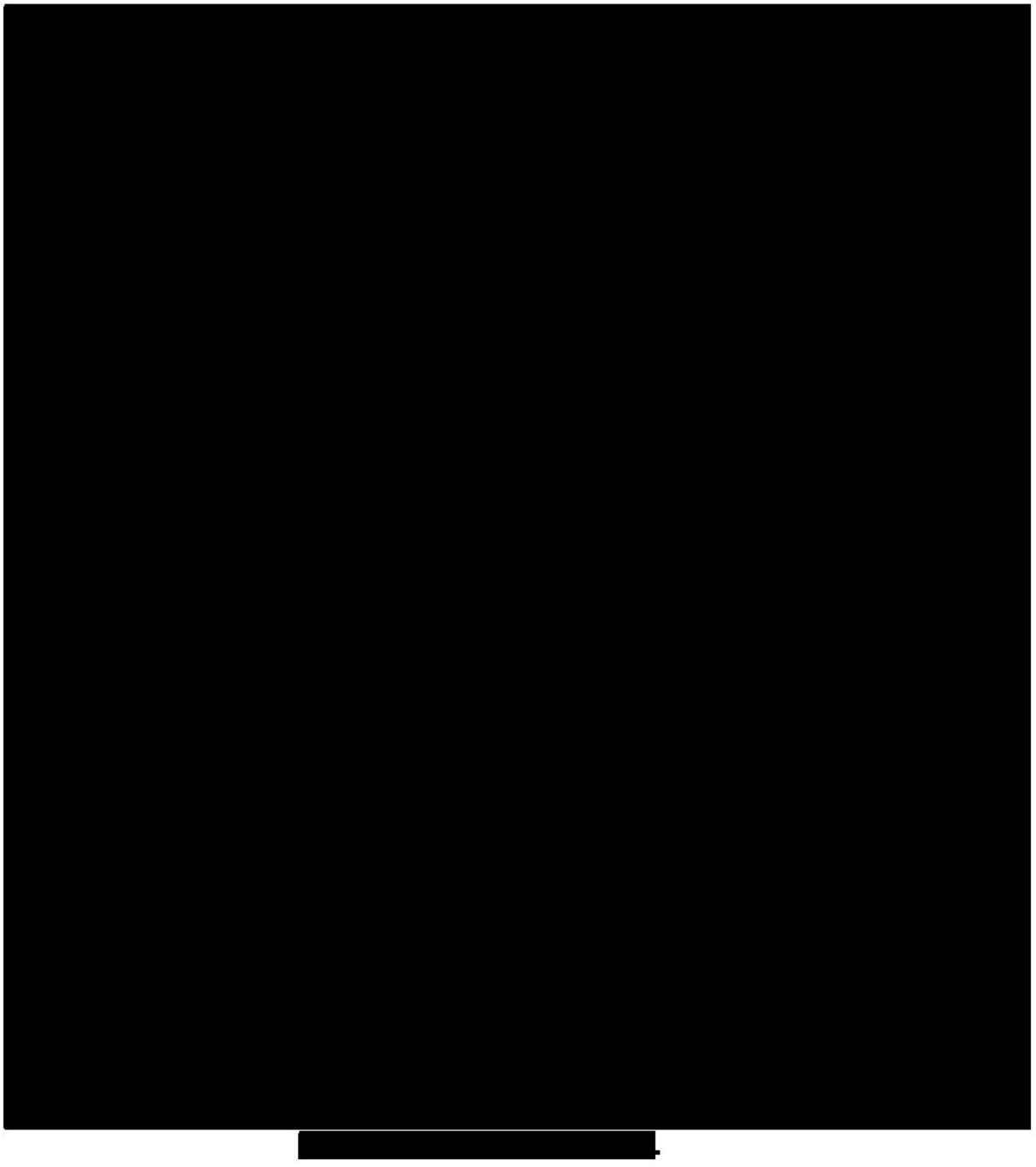












16 REFERENCE

1. Darken P, N. J. (2020). The attributable estimand: a new approach to account for intercurrent events. *Pharm Stat*, 10.1002/pst.2019

2. James, K., Bloch, D., K.K., L., Kramer, H., & Fuller , R. (1996). An index for assessing blindness in a multi-centre clinical trial. Statistics in Medicine, 15:1421–1434.

3. Mallinckrodt, C., Lin, Q., Lipkovich, I., & Molenberghs, G. (2012). A structured approach to choosing estimands and estimators in longitudinal clinical trials. *Pharm Stat*, 11(6):456-461.

4. Mallinckrodt, C., Molenberghs, G., & Rathmann, S. (2017). Choosing estimands in clinical trials with missing data. *Pharm Stat*, 16(1):29-36.

5. Rubin, D. (1987). *Multiple imputation for nonresponse in surveys.* New York, NY: John Wiley & Sons;.

6. Schade S, Mollenhauer B, Trenkwalder C. Levodopa equivalent dose conversion factors: an updated proposal including opicapone and safinamide. Mov Disord Clin Pract. 2020;7(3):343-345.