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PROTOCOL NUMBER: **BIIT0215/ NCT02587065**

PHASE OF DEVELOPMENT: 4

PROTOCOL TITLE: Multicenter interventional Phase IV study for the assessment of the effects on patient's satisfaction of Plegridy (pre-filled pen) in subjects with relapsing-remitting multiple sclerosis unsatisfied with other injectable subcutaneous Interferons. **PLATINUM STUDY** - BIIT0215

EUDRA CT NO: 2015-002201-11

DATE: 23 JULY 2015
Version Final 5.0

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Protocol BIIT0215 was approved by*:

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28/7/2015

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Biogen Italia Srl

*As per new preferred internal processes, the PLATINUM final protocol (v5.0) was signed by the Global Medical Director using electronic signatures.

By system default, these signatures are appended to the final page of the protocol, rather than to the existing signature page. For signature, turn to the final page of the protocol.

TABLE OF CONTENTS

LIST OF FIGURES

1. SPONSOR INFORMATION

This study is sponsored by Biogen Italia Srl.

Refer to Official Study Contact List for contact information.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis Of Variance
APTS	All Patients Treated Set
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CRO	Contract Research Organization
DMT	Disease Modifying Treatments
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
ET	Early Termination
FPI	First Patient In
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl-Transferase
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN	Interferon
IWRS	Interactive Web Response System
LPI	Last Patient In
LPLV	Last Patient Last Visit
MCH	Mean Cell Hemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MSTCQ	Adapted Sclerosis Treatment Concerns Questionnaire
MusiQol	Multiple Sclerosis International Quality of Life questionnaire
PHI	Protected Health Information
RBC	Red Blood Cell
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard deviation
SMPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSQM	Treatment Satisfaction Questionnaire to Medication
WBC	White Blood Cell

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	BIIT0215
Protocol Title:	Multicenter interventional Phase IV study for the assessment of the effects on patient's satisfaction of Plegridy (pre-filled pen) in subjects with relapsing-remitting multiple sclerosis unsatisfied with other injectable subcutaneous Interferons (**PLATINUM**)
Version Number:	5.0 23 July 2015
Name of Study Treatment:	Plegridy - Peginterferon beta-1a (Peg-IFN beta-1a)
Study Indication:	Relapsing-Remitting Multiple Sclerosis (RRMS)
Phase of Development:	4
Rationale for the Study:	Satisfaction with treatment has recently been included among health outcomes research variables, due to its value for health care evaluation as well as for its relevant implications in clinical practice. In fact, there is evidence that patients feeling satisfied with their treatment show better compliance with prescriptions and play an active role in their own care. The treatment based on Peg-IFN 125 µg - administered subcutaneously (SC) every 2 weeks - is effective in RRMS, it requires less-frequent injections and it is associated with a positive safety profile, comparable with that of the other currently approved first-line injectable therapies. The reduced frequency of administration might render pegylated interferon beta more tolerable, improving its convenience and providing an alternative to the established dosing regimens. This phase IV, interventional, multicenter study aims at evaluating whether Peg-IFN 125 µg administered subcutaneously (SC) every 2 weeks improves patients' satisfaction and adherence rate in RRMS subjects unsatisfied with other injectable subcutaneous Interferons. In addition, the study may provide data on Peg- IFN effects

on health-related quality of life and other relevant patients' reported outcomes.

Study Objectives and Endpoints:

Objectives

Primary:
The primary objective of the study is to investigate whether Peg-IFN beta-1a improves patients' satisfaction in RRMS subjects unsatisfied with other injectable subcutaneous Interferons, as measured by the Abbreviated Treatment Satisfaction Questionnaire to Medication (TSQM-9), across a 12-weeks observation period.

Secondary:

The secondary objectives of this study consist in the evaluation, in this study population, of the following parameters:

- effects of Peg-IFN beta-1a treatment on patients' satisfaction at 24 weeks;
- effects of Peg-IFN beta-1a treatment on short-term patients' adherence;
- impact of Peg-IFN beta-1a treatment on patient-reported health-related quality of life;
- effects of Peg-IFN beta-1a treatment on patients' fatigue;
- impact of Peg-IFN beta-1a treatment on patients' injection-system satisfaction;
- effects of Peg-IFN beta-1a on disease activity and physical disability;
- relationship between patients' satisfaction and adherence;
- relationship between patients' satisfaction and social-demographic factors (age, sex, employment working, level of education, etc) and clinical characteristics (ARR, disability, etc.)

Endpoints

Primary:

Changes from baseline in the score of convenience satisfaction domain of TSQM-9 at 12 weeks.

Secondary:

- Changes from baseline in the score of all domains of TSQM-9 at 24 weeks;
- Changes from baseline in patient adherence to treatment at 12 and 24 weeks, as evaluated by the adherence questionnaire;
- Changes from baseline in the score of FSS (Fatigue Status Scale) at weeks 12 and 24;
- Changes from baseline in the score of Adapted Sclerosis Treatment Concerns Questionnaire (MSTCQ) at weeks 12 and 24;
- Changes from baseline in the score of Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) at weeks 12 and 24;
- Changes from baseline in clinical measures (ARR, percentage of relapse-free patients, EDSS) measures at week 24.
- Incidence and severity of adverse events occurred during the study (including local tolerance to treatment at the injection site).
- Abnormalities in laboratory values.

Study Design:

This is a 6 month, open-label, single-arm, interventional, multicentric study based on patient self-administered questionnaires (as described in Methods), aimed at evaluating subject-reported effects on satisfaction with treatment of Peg-IFN beta-1a in subjects unsatisfied with other injectable, subcutaneous Interferons.

Evaluations will be performed at baseline (T0), week 12 (T1) and week 24 (T2) of treatment respectively.

Centres involved: 35, located all over Italy.

Number of visits: 3

Subjects attending the recruiting centers, meeting the eligibility criteria and signing the written Informed Consent Form (ICF) will be enrolled in the study.

Each enrolled patient will perform baseline visit (T0), visit T1(12 weeks after the start of Peg-IFN treatment) and visit T2 (24 weeks after the start of Peg-IFN treatment).

Early Termination (ET) visit will be foreseen for possible study discontinuations required by either patient's or investigator's decision.

At the baseline visit (T0), following the administration and obtainment of the signed ICF, patients will undergo the eligibility assessment according to the protocol inclusion/exclusion criteria, and the registration of socio-demographic and medical history data .

The following activities will be performed at all the study timepoints (T0, T1 and T2):

1. registration of concomitant diseases;
2. registration of concomitant medications;
3. evaluation of clinical and neurological (EDSS) conditions, adherence to treatment, occurrence of any adverse events and/or laboratory parameters abnormalities.

Moreover, at each visit patients will be administered the study questionnaires in order to evaluate:

1. Patients' satisfaction (TSMQ-9 test);
2. Patients' injection-system satisfaction (adapted MSTCQ test);
3. Patients's quality of life (MusiQoL test);
4. Patients' fatigue (FSS test).

Questionnaires will be completed electronically, by means of an i-PAD that provided by the Sponsor to the centers involved in the study. Patients unable to complete the electronic format will be supplied with paper hard copies of the questionnaires, in order to ensure proper data collection.

Rationale for Dose and Schedule Selection:	Peg-IFN beta-1a (Plegridy®) is a solution for subcutaneous injection in pre-filled pen and will be administered fortnightly at a dose of 125 mcg. The treatment involves a dose titration phase followed by a maintenance phase, according to the following scheme: Titration phase: Plegridy® 63 micrograms on day 1 of treatment Plegridy® 94 micrograms on day 14, i.e. two weeks after the first dose. Maintenance phase: Plegridy® 125 micrograms on day 28 after the first dose and then every two weeks. Patients will thus start treatment with 63 micrograms at dose 1, increasing to 94 micrograms at dose 2, reaching the full dose of 125 micrograms by dose 3 and continuing with the full dose (125 micrograms) every 2 weeks thereafter. The total duration of treatment will be of 24 weeks (titration phase and maintenance phase). Every effort should be made to administer Plegridy® at the same time and at the same day of the week.
Study Location:	The trial is planned to be performed at 35 sites in Italy, with competitive enrolment.
Number of Planned Subjects:	Approximately 275 subjects will be treated in the study.
Study Population:	This study will be conducted in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) as per 2010 McDonald criteria, with EDSS between 0.0 and 5.0 and unsatisfied with the current injectable subcutaneous Interferons. Detailed criteria are described in the protocol.
Treatment Groups:	Single arm study: All subjects enrolled after the first period (4 weeks) of dose titration will be treated with Peg IFN beta-1a 125 mcg (every 2 weeks) for a total period of 24 weeks.

Visit Schedule:	Baseline T0: start of treatment with Peg IFN beta-1a. T1: 12 weeks of treatment with Peg IFN beta-1a. T2: 24 weeks of treatment with Peg IFN beta-1a. ET (Early Termination): in case of early termination of the study. See flow chart.
Planned duration of Treatment and Follow-up:	First Subject In (FPI): Sept/2015 Last Subject In (LPI): Sept/2016 Last Subject Last Visit (LPLV): March 2017
Criteria for Evaluation:	*Inclusion criteria* $18 \leq$ Age ≤ 65 years RRMS as per 2010 McDonald criteria Baseline EDSS between 0.0 and 5.0 Treatment with injectable subcutaneous Interferons with score < 58 in the "convenience satisfaction" domain of TSQM-9 Signed informed consent Period of stability from last relapse of at least 30 days before the baseline visit. Treatment with intravenous corticosteroids completed at least 30 days before the baseline visit (assumption of oral cortisone allowed as long as within 4 mg per day for no longer than 3 days). *Exclusion criteria* Pregnancy or breast-feeding Depression or other psychiatric disorders Unwillingness or inability to comply with the protocol requirements Any contra-indications to treatment with Peg-IFN-beta 1a according to the Summary of Product Characteristics
Efficacy:	Being this is a health outcomes research study, in the present protocol the term *efficacy* is referred to the

assessment of the following patients' reported parameters, corresponding to the primary and secondary objectives of the study, and to the measurement of the related endpoints:

- overall treatment satisfaction,
- injection system satisfaction,
- adherence to treatment,
- health-related quality of life,
- fatigue.

Safety: Treatment tolerability will be assessed and all adverse events occurring during the study and changes in laboratory parameters will be collected. Also pregnancy and episodes of overdose will be collected.

Additional: Not applicable.

Statistical Methods: Descriptive statistics of T0, T1 and T2 values, of all the collected variables as well as the relevant changes from baseline will be presented as mean, and standard deviations, along with median values and ranges. The primary endpoint (change of TSQM-9 convenience domain at week 12) will be analyzed by a repeated measures analysis of variance adjusted for baseline factors (age, sex, disease duration, previous treatment duration, EDSS). The same technique will be adopted also for the analysis of the other endpoints. Correlations between variables will be assessed through the Spearman rank correlation coefficient.

Interim Analysis: No interim analysis will be performed.

Sample Size Determination: Data for estimating the sample size were derived from studies reporting the distribution (mean value and standard deviation) of the TSQM-9 in MS patients treated with IFN (9). Assuming an average value of the overall convenience domain at baseline of 55 (SD=16), 250 subjects allow a power of 90% to detect a change of 3 points on the overall convenience domain (from 55 to 58) under the conservative hypothesis of a SD=16 for the difference between baseline and week 12.

However, by assuming a drop-out rate up to 10% during the study, we consider it appropriate to enrol a total of 275 patients.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY PLATINUM -BIIT0215

4.1. Study Schematic

Figure 1: Study Design and Plan

	• Eligibility assessment • Collection of baseline data • Study drug dispensing	• Collection of on-treatment data • Study drug dispensing	• Collection of final data • Study drug accountability • Study termination
		Study drug self-administrations	
Week	0	12	24
T	0	1	2

4.2. Schedule of Events

Tests and assessment	T0 (Enrollment)	T1 (12 weeks) ± 1 week	T2 (24 weeks) ± 1 week	ET Early termination
Inclusion/Exclusion criteria	X			
Informed consent	X			
Social-demographics (e.g., age, gender)	X			
Medical history (e.g., disease duration, previous disease history and treatments)	X			
On-treatment medical information (e.g., concomitant therapies, comorbidities)	X	X	X	X
Pregnancy hCG test	X			
Clinical and neurological evaluation (including recording of relapses and EDSS)	X	X	X	X
Drug Supply	X	X		
Assessment of patients' satisfaction (TSQM-9)	X	X	X	X
Assessment of patients' adherence	X	X	X	X
Assessment of patients' injection-system satisfaction (Adapted MSTCQ)	X	X	X	X
Assessment of patients' HRQoL (MusiQoL)	X	X	X	X
Assessment of patients' fatigue (FSS)	X	X	X	X
Routine Laboratory tests	X	X	X	X
Adverse events, pregnancy exposure, episodes of overdose		X	X	X
Drug Accountability[1]		X	X	X

1. If a dose is missed, it should be administered as soon as possible, within 7 days.

5. INTRODUCTION

Multiple sclerosis is a chronic autoimmune and neurodegenerative disorder of the central nervous system characterized by inflammation, myelin destruction, and axonal damage with subsequent oligodendrocyte and neuronal loss (1).

Relapsing-remitting MS is the most common clinical presentation of the disease. Patients with relapsing MS experience discrete episodes of neurological dysfunction (referred to as relapses, exacerbations, or attacks) each lasting several days to several weeks, which occur intermittently over many years (2).

The currently available IFN-β therapies and GA both require either intramuscular (IM) or subcutaneous (SC) injections, from as few as once a week (IFN β-1a im to as many as 3 times to 4 times a week (IFN β-1a SC, IFN β-1b SC), and 7 times a week (GA SC) (3).

Despite the benefits of disease-modifying therapies (DMTs) for MS, several problems are associated with their use, including inconvenient methods and schedules of administration, long periods of therapy, and significant side effects (4).

In particular, the high frequency of injections required often produces discomfort interfering with patients' activities of daily living, and may lead to refusal or inability to accept or adhere to these therapies. In fact, the proportion of non-adherent patients on DMTs has been reported to be as high as 45%. (5, 6)

Devonshire et al. examined reasons for discontinuation of therapy in a multicenter study of adherence to IFNβ-1a im, IFNβ-1a sc , IFNβ-1b sc, and GA sc. Adherence was associated with female gender, ease of administration, satisfaction with therapy, treatment at a dedicated MS center, and family support (5).

Satisfaction with treatment is a variable recently incorporated into health outcomes research, not only due to its value for health care evaluation, but also for its implications in clinical practice. It is known that patients who are satisfied with their treatment show better compliance with prescriptions and play an active role in their own care (7).

Findings from the previous Phase 3 study (Study 105MS301) showed that the treatment based on Peg-IFN 125 µg administered subcutaneously (SC) every 2 weeks, is effective in RRMS, it requires less-frequent injections and it is associated with a positive safety profile, comparable with that of the other currently approved first-line injectable therapies (8). The reduced frequency of administration might render pegylated interferon beta more tolerable, improving its convenience and providing an alternative to the established dosing regimens.

Because MS is a life-long disease, any burden associated with treatment administration can be considered a significant component of a patients' experience of the illness. In this regard, the specific pharmacologic features of peginterferon (i.e., long half-life and low concern for accumulation) which enable the benefits outlined above to be provided with the less frequent fortnightly administration, are important to patients.

5.1. Profile of Previous Experience

Preclinical Experience with Peg-IFN

In nonclinical pharmacology studies, BIIB017 (PEGylated Interferon Beta-1a) showed an approximate 2-fold loss of potency in vitro compared to IFN β-1a in both antiviral and antiproliferative assays (Baker 2006).

As such, a dose of 63 µg BIIB017 contains 6 MIU, similar to the recommended dose of recombinant IFN β-1a IM 30 µg. PEGylation of the N-terminus of IFN β-1a with 20 kDa mPEG-O-2-methylpropionaldehyde resulted in a modified protein with improved in vivo antiangiogenic activity compared to the unmodified protein in a single-dose comparison study and similar, if not slightly greater, activity in a single- versus multiple-dose comparison study.

Safety pharmacology endpoints were included in the nonclinical, repeated-dose, Good Laboratory Practice (GLP) toxicity study in rhesus monkeys to evaluate the effects of BIIB017 on renal, respiratory, cardiovascular, gastrointestinal, and central nervous system organs.

There were no adverse BIIB017-related functional changes of any organ. There was a slight increase in the body temperature of 1°F to 2°F at 4 to 8 hours postdose that is attributable to the expected pharmacology and was not considered adverse. Histopathological evaluations of tissues did not indicate any abnormalities in any of the treatment groups.

Clinical Experience with Peg-IFN

The efficacy and safety of Peg-IFN 125 µg was assessed from the placebo-controlled first year of a 2 year randomised, double-blind, clinical study in patients with relapsing remitting multiple sclerosis (the ADVANCE study). 1512 patients were randomised to and dosed with 125 micrograms Peg-IFN 125 µg injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500)(11).

The primary endpoint was the annualized relapse rate (ARR) over 1 year. The study design and patient demographics are presented in the Table below.

No data are available from clinical efficacy/safety studies directly comparing pegylated with non-pegylated interferon beta-1a, or from patients switching between non-pegylated and pegylated interferon.

Study design	
Disease history	Patients with RRMS, with at least 2 relapses within the prior 3 years, and 1 relapse in the prior year, with an EDSS score of ≤5.0
Follow-up	1 year
Study population	83% treatment-naïve patients 47% ≥2 relapses in prior year 38% at least 1 Gd+ lesion at baseline 92% ≥9 T2 lesions baseline 16% EDSS ≥4 17% previously treated
Baseline characteristics	
Mean age (years)	37
Mean/Median disease duration (years)	3.6/2.0
Mean number of relapses within the past 3 years	2.5
Mean EDSS score at baseline	2.5

EDSS: Expanded Disability Status Scale
Gd+: Gadolinium-enhancing

Peg-IFN 125 µg every 2 weeks significantly reduced the annualized relapse rate (ARR) by 36% compared to placebo (p=0.0007) at one year (see Table below) with consistent reductions of the ARR noted in subgroups defined by demographic and baseline disease characteristics. Peg-IFN 125 µg also significantly reduced the risk of relapse by 39% (p=0.0003), the risk of sustained disability progression confirmed at 12 weeks by 38% (p=0.0383) and at 24 weeks (post-hoc analysis) by 54% (p=0.0069), the number of new or newly enlarging T2 lesions by 67% (p<0.0001), the number of Gd-enhancing lesions by 86% (p<0.0001) and the number of T1 hypointense lesions compared to placebo by 53% (p<0.0001). A treatment effect was observed as early as 6 months, with Peg-IFN 125 µg every 2 weeks demonstrating a 61% reduction (p<0.0001) in new or newly enlarging T2 lesions as compared with placebo. Across relapse and MRI endpoints Peg-IFN 125 µg every two weeks showed a numerically greater treatment effect over the Peg-IFN 125 µg every four weeks dosing regimen at year 1.

Results over 2 years confirmed that efficacy was maintained beyond the placebo controlled first year of the study. Patients exposed to Peg-IFN 125 µg every 2 weeks showed statistically significant reductions compared to patients exposed to Peg-IFN 125 µg every 4 weeks over 2 years in a post-hoc analysis for endpoints including ARR (24%, p=0.0209), the risk of relapse (24%, p=0.0212), the risk of disability progression with 24 week confirmation (36%, p=0.0459), and MRI endpoints (new/enlarging T2 60%, Gd+ 71%, and T1 hypointense lesions 53%; p<0.0001 for all).

Results for this study are shown in the Table below

	Placebo	Plegridy 125 micrograms every 2 weeks	Plegridy 125 micrograms every 4 weeks
Clinical endpoints			
N	500	512	500
Annualised relapse rate	0.397	0.256	0.288
Rate ratio 95% CI P-value		0.64 0.50 – 0.83 p=0.0007	0.72 0.56 – 0.93 p=0.0114
Proportion of subjects relapsed	0.291	0.187	0.222
HR 95% CI P-value		0.61 0.47 – 0.80 p=0.0003	0.74 0.57 – 0.95 p=0.020
Proportion with 12 week confirmed disability progression*	0.105	0.068	0.068
HR 95% CI P-value		0.62 0.40 – 0.97 p=0.0383	0.62 0.40 – 0.97 p=0.0380
Proportion with 24-week confirmed disability progression*	0.084	0.040	0.058
HR 95% CI P-value		0.46 (0.26 – 0.81) p=0.0069	0.67 (0.41 – 1.10) p=0.1116
MRI endpoints			
N	476	457	462
Mean [Median] no. of new or newly enlarging T2 hyperintense lesions (range)	13.3 [6.0] (0 – 148)	4.1 [1.0] (0 – 69)	9.2 [3.0] (0 – 113)
lesion mean ratio (95% CI) P-value		0.33 (0.27, 0.40) p≤0.0001	0.72 (0.60, 0.87) 0.0008
Mean [Median] no. of Gd-enhancing lesions (range)	1.4^ [0.0] (0 – 39)	0.2 [0.0] (0 – 13)	0.9 [0.0] (0 – 41)
% reduction vs placebo P-value		86 p<0.0001	36 p=0.0738
Mean [Median] no. of new T1 hypointense lesions (range)	3.8 [1.0] (0 – 56)	1.8 [0.0] (0 – 39)	3.1 [1.0] (0 – 61)
% reduction vs placebo P-value		53 p<0.0001	18 0.0815

HR: Hazard ratio CI: Confidence interval * Sustained disability progression was defined as at least a 1 point increase from baseline EDSS ≥ 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 / 24 weeks. ^n=477

Patients who failed previous MS treatment were not included in the study.

Subgroups of patients with higher disease activity were defined by relapse and MRI criteria as reported below, with the following efficacy results:

- For patients with ≥1 relapse in the previous year and ≥9 T2 lesions or ≥1 Gd+ lesion (n=1401), the annual relapse rate at 1 year was 0.39 for placebo, 0.29 for Peg-IFN 125 µg every 4 weeks and 0.25 for Peg-IFN 125 µg every 2 weeks.

Results in this subgroup were consistent with those in the overall population

- For patients with ≥2 relapses in the previous year and at least 1 Gd+ lesion (n=273), the annual relapse rate at 1 year was 0.47 for placebo, 0.35 for Peg-IFN 125 µg every 4 weeks, and 0.33 for Peg-IFN 125 µg every 2 weeks.

Results in this subgroup were numerically consistent with those in the overall population but not statistically significant.

5.2. Study Rationale

Satisfaction with treatment is a variable recently incorporated into health outcomes research, not only due to its value for health care evaluation, but also for its implications in clinical practice. It is known that patients who are satisfied with their treatment show better compliance with prescriptions and play an active role in their own care. Adherence to treatment is also important because it is associated with better clinical and economic outcomes, including lower risks for MS relapse and MS-related hospitalization, and with lower MS-related medical costs.

Several studies show that administration of interferon formulations using an autoinjector can increase satisfaction and/or convenience in patients with MS. In fact, as shown by a significant observation conducted on 2.648 RRMS patients (3), the identification of factors that affect adherence to prescribed treatments is the first step in improving adherence of patients with MS to therapy, thereby helping maximize the benefits of long-term DMTs. According to the results of this study, the most common reasons for non-adherence were forgetting to administer the injection (50.2%) and other injection-related reasons (32.0%). Moreover, the abovementioned investigation showed that adherent patients reported better quality of life ($P < 0.05$) and fewer neuropsychological issues ($P < 0.001$) than non-adherent patients.

The treatment based on Peg-IFN 125 µg, administered subcutaneously (SC) every 2 weeks, is effective in RRMS, and it requires less-frequent injections and is associated with a positive safety profile at least comparable with that of the other currently approved first-line injectable subcutaneous Interferons. The improved convenience that would be expected with reduced injection frequency might render pegylated interferon beta more tolerable and may provide an alternative to the established dosing regimens, thus leading to improvements in both patients' satisfaction and compliance.

By virtue of the abovementioned background information, the general objective of this study is to provide valuable information on the effects of Peg-IFN beta-1a in terms of users' satisfaction and adherence to treatment, thus representing an actual alternative for patients unsatisfied with the current

injectable subcutaneous Interferons. In such a context, as a primary objective this phase IV, interventional, multicenter study aims at evaluating if Peg-IFN 125 μg subcutaneous (SC) every 2 weeks improves satisfaction and adherence in RRMS patients unsatisfied with others injectable subcutaneous Interferons. In addition, the study may provide data on Peg-IFN effects on health-related quality of life and other relevant patients' reported outcomes.

5.3. Rationale for Dose and Schedule Selection

Peg-IFN at a dose of 125 μg, administered subcutaneously every 2 weeks is a registered product (Plegridy®), specifically indicated in adult patients for the treatment of relapsing remitting multiple sclerosis. Being this a post-authorization study, thus conducted according to the registered indication of the marketed product, study dose and schedule selection are compliant with those recorded on the product Summary of Product Characteristics (SMPC).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

The primary objective of this study is to investigate whether Peg-IFN beta-1a improves the satisfaction of RRMS patients unsatisfied with injectable subcutaneous Interferons, as measured by the Abbreviated Treatment Satisfaction Questionnaire to Medication (TSQM-9), at 12 weeks.

6.1.2. Secondary Objectives

The secondary objectives of this study are to evaluate in this study population:

- effects of Peg-IFN beta-1a treatment on patients' satisfaction at 24 weeks;
- effects of Peg-IFN beta-1a treatment on short-term patients' adherence;
- effects of Peg-IFN beta-1a treatment on patients' fatigue;
- effects of Peg-IFN beta-1a on disease activity and physical disability;
- impact of Peg-IFN beta-1a treatment on patient-reported health-related quality of life;
- impact of Peg-IFN beta-1a treatment on patients' injection-system satisfaction;
- Evaluate the relationship between patients' satisfaction and adherence;
- Evaluate the relationship between patients' satisfaction and social-demographic factors (age, sex, employment working, level of education, etc) and clinical characteristics (ARR, disability, etc.)
- Evaluate the treatment safety and tolerability.

6.2. Endpoints

6.2.1. Primary Endpoint

Changes from baseline in the score of convenience satisfaction domain of TSQM-9 at 12 weeks.

6.2.2. Secondary Endpoints

• Changes from baseline in the score of all domains of TSQM-9 at 24 weeks;

• Changes from baseline in patient adherence to study treatment survey at 12 and 24 weeks;

• Changes from baseline in the score of FSS (Fatigue Status Scale) at 12 and 24 weeks;

• Changes from baseline in the score of Adapted Sclerosis Treatment Concerns Questionnaire (MSTCQ) at 12 and 24 weeks;

• Changes from baseline in the score of Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) at 12 and 24 weeks;

- Changes from baseline in clinical measures (ARR, percentage of relapse-free patients), measures at 24 weeks.
- Incidence and severity of adverse events occurred during the study (including local tolerance to treatment at the injection site).
- Abnormalities in laboratory values.

7. STUDY DESIGN

7.1. Study Overview

This is a 6 month, phase IV, open-label, single-arm, interventional, multicentric study, based on self-administered questionnaires (as described in Methods) and aimed at evaluating patient-reported effects on user's satisfaction of Peg-IFN beta-1a therapy on patients unsatisfied with other injectable, subcutaneous Interferons. The relevant evaluations will be performed at baseline, week 12 and week 24.

Informed consent will be obtained at baseline prior to study enrolment and before collection of all relevant clinical information (i.e., relapses, EDSS).

Clinical evaluation and questionnaire administration will be performed at baseline (within 2 weeks before Peg-IFN beta-1a therapy onset) and after 12 and 24 weeks.

Subjects may elect to discontinue from study treatment at any time, due to medical reasons (contraindications, medical conditions that necessitate drug discontinuation according to the Investigator) or at personal and/or Investigator's discretion. In all cases, reasons for discontinuation from investigational treatment or withdrawal from the study will be recorded in the subject's CRF.

All relevant and required information about any adverse event (serious and non-serious), including laboratory abnormalities and about pregnancy and cases of overdose occurring during the study will be collected and registered in the subject's CRF.

In case of SAE, pregnancy, or cases of overdose, the Investigator will have to notify Biogen Italia Srl's Drug Safety Unit immediately and no later than 24 hours from its occurrence, by fax or e-mail. Any event follow-up will have to be notified to Biogen Italia's Drug Safety Unit within 24 hours from its recording.

7.2. Overall Study Duration and Follow-Up

The overall study duration will be of 24 weeks, inclusive of baseline evaluation and treatment phase.

7.2.1. Screening

Subject eligibility for the study will be determined at baseline visit.

7.2.2. Treatment

Each eligible subject will refer to the relevant recruitment study site to receive the study treatment every two weeks for the overall study period (24 weeks). Study drug dispensing is foreseen at T0 and T1 respectively.

7.3. Study Stopping Rules

Biogen Italia Srl may terminate this study at any time, after informing Investigators. Investigators will be notified by Biogen Italia Srl or CRO if the study is placed on hold, completed, or closed.

7.4. End of Study

The end of study corresponds to the date of the last subject's last visit, for final collection of data for the evaluation of the primary endpoint of the study.

8. STUDY POPULATION

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Baseline (T0):

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Aged between 18 and 65 years old inclusive, at the time of informed consent.
3. Subjects diagnosed with Relapsing Remitting MS according to 2010 McDonald criteria.
4. Subjects with EDSS score between 0.0 and 5.0 at baseline.
5. Treatment with injectable subcutaneous Interferons with score < 58 in the "convenience satisfaction" domain of TSQM-9.
6. Period of stability from last relapse of at least 30 days before the baseline visit.
7. Treatment with intravenous corticosteroids completed at least 30 days before the baseline visit (assumption of oral cortisone allowed as long as within 4 mg per day for no longer than 3 days).

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Baseline T0:

1. Pregnancy or breast-feeding.
2. Depression or other psychiatric disorders.
3. Unwillingness or inability to comply with the requirements of the protocol.
4. Have any contra-indications to treatment with Peg-IFN-beta 1a according to the Summary of Product Characteristics.

9. ENROLLMENT PROCEDURES

Once the investigational site has been activated, participants' enrolment may start, according to the inclusion/exclusion criteria described in the previous sections 8.1 and 8.2.

Subjects must be administered the Informed Consent before any screening tests or assessments are performed. At the time of consent, the subject will be enrolled into the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.1. Registration of Subjects

As the study is a single arm, open label one, no randomization procedure is provided and patients will be assigned an identification code inclusive of a progressive number linked to the center number.

10. TREATMENT OF SUBJECTS

[redacted] will provide the Investigational Product to the recruiting sites in Italy.

Refer to Section 11 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

10.1. Study Treatment Schedule and Administration

The recommended dosage of Peg-INF is 125 micrograms injected subcutaneously every 2 weeks.

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1, increasing to 94 micrograms at dose 2, reaching the full dose of 125 micrograms by dose 3 and continuing with the full dose (125 micrograms) every 2 weeks thereafter (see Table below). An Initiation Pack is available containing the first 2 doses (63 micrograms and 94 micrograms).

Titration schedule at initiation Dose	Time*	Amount (micrograms)	Pen label
Dose 1	Day 1	63	Orange
Dose 2	Week 2	94	Blue
Dose 3	Week 4 (and thereafter)	125 (full dose)	Grey

*Dosed every 2 weeks

Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Prophylactic and concurrent use of anti-inflammatory, analgesic and/or antipyretic treatments may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment.

If a dose is missed, it should be administered as soon as possible.

• If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.

• If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose. A patient should not administer two doses of Peg-INF within 7 days of each other.

Refer to Section 4.1 for a schematic on the study design.

10.2. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

Subjects enrolled should be instructed by site staff to return used and unused pens to the site for accountability.

10.3. Continuation of Treatment

No further provisions are made for access to the study treatment.

10.4. Concomitant Therapy

The investigator and/or study personnel will record all concomitant medications taken by the subject during the study from the date of signature of informed consent. Any medications considered necessary for the subject's welfare, and which will not interfere with the study medication, may be given at the discretion of the investigator. Administration of all concomitant medications must be reported in the appropriate section of the CRF along with dosage information, dates of administration and reasons for use. The following conditions should be addressed by the investigator with particular attention, documenting specifically the reasons for the administration of a concomitant medication for the following cases:

- For a MS related condition (e.g. pain, fatigue or weakness and relapses).
- Recording Concomitant Medication from 30 days before baseline.

No interaction studies have been performed. The clinical studies indicate that multiple sclerosis patients can receive Plegridy and corticosteroids during relapses. Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Plegridy is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. antiepileptics and some classes of antidepressants.

11. STUDY TREATMENT MANAGEMENT

Study treatment must be stored in a secure location. Accountability for study treatment is responsibility of the Investigator. More details concerning this responsibility are included in Section 11.2.

Study treatment must only be dispensed by a Pharmacist or appropriately trained staff.

Study treatment is to be dispensed only to subjects enrolled in this study.

The study treatment is supposed to be self-administered by the enrolled subjects. Study site staff should train enrolled subjects in the proper technique for self-administering subcutaneous injections using the prefilled pen.

Subjects should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections are abdomen, back of the upper arm, and thigh.

Study site staff and enrolled subjects should refer to the approved package insert for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

11.1. Peg –IFN (PLEGRIDY®)

Plegridy® is supplied in a single-use, disposable, pre-filled pen that uses a spring-driven mechanism. The following doses of 20 kDa mPEG-O-2-methylpropionaldehyde-modified human IFN β-1a in 20 mM acetic acid/sodium acetate buffer pH 4.8, 150 mM arginine hydrochloride, and 0.005% Polysorbate 20 are provided:

-63 micrograms of peginterferon beta-1a in 0.5 mL solution for the first injection.
-94 micrograms of peginterferon beta-1a in 0.5 mL solution for the second injection
-125 micrograms of peginterferon beta-1a in 0.5 mL solution for the subsequent injections.

The label will include conditions for storage, lot number, and other pertinent information.

11.1.1. Plegridy® Preparation

The individual preparing Plegridy® should first carefully review the instructions provided in the approved package insert.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the prefilled pen or drug, it should not be used. The pen in question should be saved at the study site and the problem immediately reported to Biogen Italia.

Plegridy® is to be stored at 2°C to 8°C, in a monitored, locked refrigerator with limited access.

Plegridy® must not be frozen; it has to be stored in the refrigerator at 2°C-8°C and stored in the original package in order to be protected from light. Plegridy® can be stored at room temperature (2°C to 25°C) for up to 30 days as long as it is stored away from light. If Plegridy® is at room temperature for more than30 days, it should not be used and must be returned to the Investigator.

The Investigator must return all unused pre-filled pens of Plegridy® as instructed by Biogen Italia

If any Plegridy supplies are to be destroyed at the site, the institution/Principal Investigator(s) must obtain prior approval by Biogen Italia. After such destruction, the institution/Principal Investigator(s)

must notify Biogen Italia, in writing, of the method of destruction, the date of destruction, and the location of destruction.

11.2. Plegridy® Accountability

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), amount returned by the subject, and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all pens both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of Plegridy® supplied, dispensed, and subsequently returned to Biogen Italia. A written explanation must be provided for any discrepancies.

12. DISCONTINUATION FROM STUDY TREATMENT AND/OR STUDY WITHDRAWAL

12.1 Discontinuation from study treatment

A subject *must* permanently discontinue from Peg-IFN for any of the following reasons:

- The subject becomes pregnant.
- The subject withdraws consent.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.
- Lost to follow up.

The reason for discontinuation from study treatment must be recorded in the subject's CRF.

All efforts must be made by the Investigator to perform the Early Termination Visit (ET visit) to Subjects discontinuing from treatment. However, the ET visit form will have to be filled by the investigator also for patients that are lost to follow up.

Subjects discontinuing from study treatment for any of the abovementioned reasons must be permanently withdrawn from the study.

12.2 Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- The subject meets any of the criteria defined in Section 12.1
- The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

13. EFFICACY ASSESSMENTS

13.1. Evaluations concerning the patients' adherence, quality of life, injection-system satisfaction, through the specific tests, including MSTCQ and MusiQoL.

Being this a health outcomes research study, in the present protocol the term *efficacy* refers to the assessment of the following patients' reported parameters, corresponding to the primary and secondary objectives of the study, and to the measurement of the related endpoints:

- overall treatment satisfaction;
- injection system satisfaction;
- adherence to treatment;
- health-related quality of life;
- fatigue.

Demographic (age, gender, education and employment) and medical information (disease duration, previous treatments, comorbidities and concomitant therapies, EDSS score and number of relapses in the previous 12 months) will be obtained at baseline.
All the endpoint-related questionnaires, described below, will be administered at baseline and after 12 and 24 weeks of treatment.

a) Patients' Satisfaction assessment
- *Abbreviated Treatment Satisfaction Questionnaire to Medication (TSQM-9)*

The TSQM Version 1.4 is a 14-item psychometrically robust and validated instrument consisting of four scales. The 14 questions were selected from an original set of 55 questions obtained from literature review and focus groups. The four scales of the TSQM include the effectiveness scale (questions 1 to 3), the side effects scale (questions 4 to 8), the convenience scale (questions 9 to 11) and the global satisfaction scale (questions 12 to 14). In the TSQM-9, the five items related to side effects of medication were not included, which creates a need to psychometrically assess the performance of the abbreviated instrument. The TSQM-9 domain scores were calculated as recommended by the instrument authors (10). The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

b) Patients' adherence assessment

A questionnaire assessing adherence and the reasons for not taking drug at the recommended frequency of administration.

c) Patients' Injection-System Satisfaction
- *Adapted Sclerosis Treatment Concerns Questionnaire (MSTCQ)*

The MSTCQ is a validated 20-item patient questionnaire developed to address patient concerns with IFN-beta treatment that are not related to efficacy. It has two domains: injection-system satisfaction and side effects. The side-effects domain comprises 3 subscales: ISRs, global side effects, and FLS.11 All questions in the MSTCQ have a 5-point response choice, with lower total scores indicating better outcomes. A version adapted for Plegridy will be used.

d) Health Related Quality of Life

- *Multiple Sclerosis International Quality of Life questionnaire (MusiQoL)*

MusiQoL version 5.2 (Multiple Sclerosis International Quality of Life) is a multi-dimensional self-administered questionnaire consisting of 31 items describing nine dimensions of health-related quality of life. The nine dimensions assess many aspect of QoL that are specific to MS patients (activities of daily living, psychological wellbeing, symptoms, relationship with friends, relationship with family, sentimental and sexual life, coping rejection, relationship with healthcare system). Items listed in the MusiQoL questionnaire have responses describing frequency/extent of an event on a five-point scale ranging from never/not at all (option 1) to always/very much (option 5). All of the 9 dimensions and the global index are linearly transformed and standardized on a 0-100 scale. Higher scores indicate a better level of health-related QoL for each dimension and for the global index score.

e) Patients' Fatigue

- *Fatigue Severity Scale (FSS)*

This is a specific questionnaire composed of 9 statements on the state of fatigue during the previous week. The answers are within a scale of agreement ranging from 1 to 7, with 1 representing the lowest level of agreement. An overall score of ≥36 indicates a state of fatigue.

Refer to Section 4.2 for the timing of assessments.

13.2. Laboratory Efficacy Assessments

There are no specific laboratory tests but it is the responsibility of the investigator to perform routine tests and to monitor the relevant results in order to evaluate the effects of the ongoing treatment with Peg-IFN.

14. SAFETY ASSESSMENTS

14.1. Clinical Safety Assessments

The following safety assessments are provided by the clinical protocol (Refer to Section 4.2 for the relevant timing):

- Medical History
- Physical examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate
- Weight
- Concomitant therapy and procedure recording
- AE and SAE (including laboratory abnormalities), pregnancy and cases of overdose recording

In addition, routine clinical assessments will be performed in order to check the safety of the Peg-IFN ongoing treatment.

14.2. Laboratory Safety Assessments

At the Investigator's discretion, the following routine laboratory tests can be carried out, in order to monitor the safety profile of the ongoing treatment based on Peg-IFN:

- Hematology: RBC- WBC –Haemoglobin- Haematocrit- MCV- MCH – MCHC - Platelets Count –Lymphocytes- Monocytes – Neutrophils – Eosinophils – Basophils
- Blood chemistry: creatinine, blood urea nitrogen (BUN), alkaline phosphatase, ALT, AST, gamma-glutamyl-transferase (GGT).

A pregnancy hCG test (blood sample) will be performed at the baseline visit (T0) to exclude pregnancy, if applicable (it is not required if the subject is post-menopausal or surgically sterilized).

Refer to Section 4.2 for the timing of assessments.

14.3. Product-Specific or Study-Specific Safety Assessments

Being this a Phase IV study, the investigational treatment will be administered according to the SMPC indications as done for routine practice and thus no additional specific tests are foreseen under this protocol.

15. SAFETY DEFINITIONS, MONITORING AND REPORTING

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for serious adverse event (SAE) reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

15.1.2. Adverse Event

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

15.1.3. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death
- in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

A SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

In addition, terms listed on the Biogen Medically Significant Terms List should always be considered SAEs based on medical judgment (Appendix G).

15.2. Monitoring and Recording Events

15.2.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF, but before administration of study treatment is to be recorded on the e-CRF and on the SAE Form, and faxed or sent by email to Biogen Italia Drug Safety Unit within 24 hours of the study site staff becoming aware of the event (see Section 15.2.5).

15.2.2. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the end of the study is to be recorded on the e-CRF, regardless of the severity of the event or its relationship to study treatment.

Any AE experienced by the subject between the time of signing the ICF and the end of the study is to be recorded on the e-CRF, regardless of the severity of the event or its relationship to study treatment.

15.2.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the first dose of study treatment and the end of the study is to be recorded on the e-CRF and on the SAE Form and faxed or sent by email to Biogen Italia Drug Safety Unit, regardless of the severity of the event or its relationship to study treatment.

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

Subjects will be followed for all SAEs until 4 weeks after the last dose of treatment. Thereafter, the event should only be recorded if the Investigator considers it related to study treatment.

15.2.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

15.2.5. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the Biogen Italia Drug Safety Unit within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any Serious Event that occurs between the time that the subject has signed informed consent and the patient final study visit must be reported to the Biogen Italia Drug Safety Unit within 24 hours of the study site staff becoming aware of the event. After 4 weeks after the last dose, **the event should only be recorded if the Investigator considers it related to study treatment**.

A report ***must be submitted*** to Biogen Italia Drug Safety Unit regardless of the following:

- whether or not the subject has undergone study-related procedures
- whether or not subject has received study treatment
- the severity of the event
- the relationship of the event to study treatment

To report initial or follow-up information on a Serious Event, a completed SAE form has to be sent to the following:

Fax: [redacted]

Or

e-mail: [redacted]

15.2.5.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate e-CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen Italia Drug Safety Unit.

15.3. Safety Classifications

15.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to commercial drug	
Not related	An adverse event will be considered "not related" to the use of the investigational drug if there is not a possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.
Related	An adverse event will be considered "related" to the use of the investigational drug if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.

15.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.3.3. Expectedness of Events

Like all medicines, Peg-IFN (Plegridy®) can cause side effects, although not everybody gets them. In accordance with the clinical experience of the marketed product, the following events may occur to Peg-INF (Plegridy®) users:

Serious side effects

- Liver problems
- Depression
- Serious allergic reaction
- Seizures
- Injection site damage
- Kidney problems including scarring that may reduce your kidney function

- Blood problems

- Other side effects (very common side effects, flu-like symptoms, nausea or vomiting, pruritus, hives).

15.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered a SAE, even if the subject is hospitalized; the study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on the e-CRF and on the Overdose Form and faxed to Biogen Italia Drug Safety Unit within 24 hours, to the number [redacted]. The form can be sent to Biogen Idec Italia also via email, to the email address [redacted].

An overdose should be reported even if it does not result in an AE.

15.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the Biogen Italia Medical Director, Drug Safety Unit Responsible, or CRO.

15.5.3. Contraception Requirements

All subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for at least 2 weeks after their last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy.
- Posthysterectomy.

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, cervical cap).
- Abstinence can be considered an acceptable method of contraception at the discretion of the Investigator. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

For males:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms with spermicide.

15.5.4. Pregnancy

If a subject (or a male subject's partner) becomes pregnant during the study, she/he must refer it immediately to the Investigator.

If a subject becomes pregnant during the study, the Investigator should stop the treatment and refer to the Plegridy® package insert for further guidance. The Investigator must enter the case of pregnancy in the e-CRF and in the appropriate Form and report it to Biogen Italia Drug Safety Unit, by faxing or e-mailing the appropriate form within 24 hours of the study site staff becoming aware of the pregnancy, at [redacted] or [redacted]. The Investigator or study site staff must report the outcome of the pregnancy to the Biogen Italia Drug Safety Unit.

Please note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported when conception occurred during the study treatment period.

15.5.5. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Biogen Italia Drug Safety Unit will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to Biogen Idec procedures and to local laws.

15.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs and laboratory abnormalities, regardless of the severity or relationship to study treatment and monitor and record all cases of overdose.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.

- Complete a SAE form for each serious event and send it by fax or email to the Biogen Italia Drug Safety Unit within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Biogen Italia Drug Safety Unit within 24 hours of the study site staff becoming aware of new information and entered in the e-CRF.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs to local ethics committees, as required by local law.

15.7. Biogen Italia Responsibilities

Biogen Italia's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen Italia is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives and Endpoints

Study objectives and related endpoints are described in Section 6

16.1.1. Primary Objective and Endpoint

The primary objective of this study is to investigate whether Peg-IFN beta-1a improves the satisfaction of RRMS patients unsatisfied with injectable subcutaneous Interferons, as measured by the Abbreviated Treatment Satisfaction Questionnaire to Medication (TSQM-9), at 12 weeks.

The primary endpoint is to evaluate the changes from baseline in the score of convenience satisfaction domain of TSQM-9 at 12 weeks

16.1.2. Secondary Objectives and Endpoints

The secondary objectives are:

- to evaluate the effects of Peg-IFN beta-1a treatment on patients' satisfaction at 24 weeks;
- to evaluate the effects of Peg-IFN beta-1a treatment on short-term patients' adherence;
- to evaluate the effects of Peg-IFN beta-1a treatment on patients' fatigue;
- to evaluate the effects of Peg-IFN beta-1a on disease activity and physical disability;
- to evaluate the impact of Peg-IFN beta-1a treatment on patient-reported health-related quality of life;
- to evaluate the impact of Peg-IFN beta-1a treatment on patients' injection-system satisfaction;
- to evaluate the relationship between patients' satisfaction and adherence;
- to evaluate the relationship between patients' satisfaction and social-demographic factors (age, sex, employment working, level of education, etc) and clinical characteristics (ARR, disability, etc.)
- to evaluate the treatment safety and tolerability.

In relation to the primary objectives listed above the following secondary measures will be evaluated:

- Changes from baseline in the score of all domains of TSQM-9 at 24 weeks;
- Changes from baseline in patient adherence to study treatment survey at 12 and 24 weeks;
- Changes from baseline in the score of FSS (Fatigue Status Scale) at 12 and 24 weeks;
- Changes from baseline in the score of Adapted Sclerosis Treatment Concerns Questionnaire (MSTCQ) at 12 and 24 weeks;

• Changes from baseline in the score of Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) at 12 and 24 weeks;

• Changes from baseline in clinical measures (ARR, percentage of relapse-free patients), measures at 24 weeks.

• Incidence and severity of adverse events occurred during the study (including local tolerance to treatment at the injection site).

• Abnormalities in laboratory values.

16.2. Demography and Baseline Disease Characteristics

All the collected data will be summarized at baseline. Continuous variables will be summarized by the mean, standard deviation, median, range and interquartile range. Frequency distributions will be used to summarize categorical variables

16.3. Efficacy Data

16.3.1. Analysis Population

Efficacy population = Full Analysis Set (FAS) consisting of all enrolled patients who took at least one dose of the study medication.

16.3.2. General Methods of Analysis

The primary and secondary endpoints will be evaluated using a repeated measures ANOVA. The repeated measures ANOVA is used to compare group means on a dependent variable across repeated measurements of time. This statistical method is used for making simultaneous comparisons between two or more means of two or more related, not independent, groups.

However, in addition, it could be useful to apply a general linear mixed model that models for group means as fixed effects while simultaneously modeling for individual subject variables as random effects (12).

This kind of model is a subject-specific model and is a choice for analysing longitudinal data.

Unlike the repeated measures ANOVA, which requires a complete balanced array of data, the mixed model can accommodate a dataset with a large portion missing. Although the repeated measures ANOVA requires a fixed time schedule among all individual units, the mixed model can accommodate flexible time schedules. Furthermore, rather than treating time as a categorical variable, as in the repeated measures ANOVA, the mixed model is capable of treating time as either a continuous variable or a categorical variable or both.

Spearman's correlation coefficient measures the strength of association between two ranked variables.

Differences will be considered statistically significant if the p-value will be less or equal to a type I error =0.05 (two-sided test).

16.3.3. Primary Endpoint Analysis

The primary endpoint (change of TSQM-9 convenience domain at week 12) will be analysed by a repeated measures analysis of variance adjusted for baseline factors (age, sex, disease duration, previous treatment duration, EDSS).

16.3.4. Secondary Endpoints Analysis

All the other endpoints will be analysed according to the same technique. Correlations between variables will be assessed by a Spearman rank correlation coefficient.

To evaluate the relationship between patients' satisfaction and social-demographic factors (age, sex, employment working, level of education, etc.) and clinical characteristics (ARR, disability, etc.) generalized linear mixed models for repeated measurements will be performed.

16.4. Safety Data

16.4.1. Analysis Population

Safety population = All Patients Treated Set (APTS), consisting of all enrolled patients who took at least one dose of study medication;

16.4.2. Methods of Analysis

Adverse events

All events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Type and incidence of all AEs will be tabulated. Severity and drug relatedness of all reported AEs will be tabulated.

Clinical Laboratory Tests

For the clinical laboratory data, descriptive statistics will be generated for all tests performed. Laboratory abnormalities will be determined in accordance with the normal ranges of the clinical laboratory. Laboratory abnormalities will be tabulated.

16.5. Sample Size Considerations

Data for estimating the sample size were derived from studies reporting the distribution (mean value and standard deviation) of the TSQM-9 in MS patients treated with IFN (9). Assuming an average value of the overall convenience domain at baseline of 55 (SD=16) (9), with 250 subjects we have a power of 90% to detect a change of 3 points on the overall convenience domain (from 55 to 58) under the conservative hypothesis of a SD=16 (9) for the difference between baseline and week 12. However, by assuming a drop-out rate up to 10% during the study, we consider it appropriate to enrol a total of 275 patients.

17. ETHICAL REQUIREMENTS

Biogen Italia and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

The Investigator and Biogen Italia must adhere to the principles set forth by the Declaration of Helsinki dated October 2013.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Investigator makes any changes to the ICF, Biogen Italia must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen Italia. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen Italia.

It is the responsibility of the Principal Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen Italia must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and Biogen Italia.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen Italia.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen Italia to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law.

The subject will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. Biogen Italia, its partner(s) and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen Italia maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen Italia will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen Italia or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen Italia or the regulatory authorities may wish to perform on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Principal Investigator(s) must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

CRFs will be used as source data for data collected through questionnaires and scales administered to the subjects, whether filled in by the patient using the i-PAD or paper format.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen Italia Srl is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, CRO and Biogen Italia.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Web Response System

The WebEZ IWRS system provided by [redacted] will be used in this study. Before subjects are screened or enrolled, [redacted] will provide each study site with appropriate training and a user manual.

19.1.3. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed and supported by the CRO – [redacted] and configured by Biogen Italia.

19.2. Study Committees

Not applicable.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and Regulatory Authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen Italia may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the subject consent form may require similar modifications (see Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen Italia in writing and receive written authorization from Biogen Italia to destroy study records. In addition, the Investigator must notify Biogen Italia of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen Italia will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen Italia.

20. REFERENCES

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Mult Scler. 2014 Nov 28. pii: 1352458514557986

12) Charlene Krueger and Lili Tian, A Comparison of the General Linear Mixed Model and Repeated Measures ANOVA Using a Dataset with Multiple Missing Data Points Biol Res Nurs October 2004 6: 151-157, doi:10.1177/1099800404267682

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Multicenter interventional Phase IV study for the assessment of the effect of Plegridy (pre-filled pen) on satisfaction in patients with relapsing-remitting multiple sclerosis unsatisfied with others injectable subcutaneous Interferons. PLATINUM STUDY," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

22. APPENDICES:

Appendix A EDSS: Expanded Disability Status Score

Appendix B TSQM9: Abbreviated Treatment Satisfaction Questionnaire to Medication

Appendix C Treatment Adherence Assessment

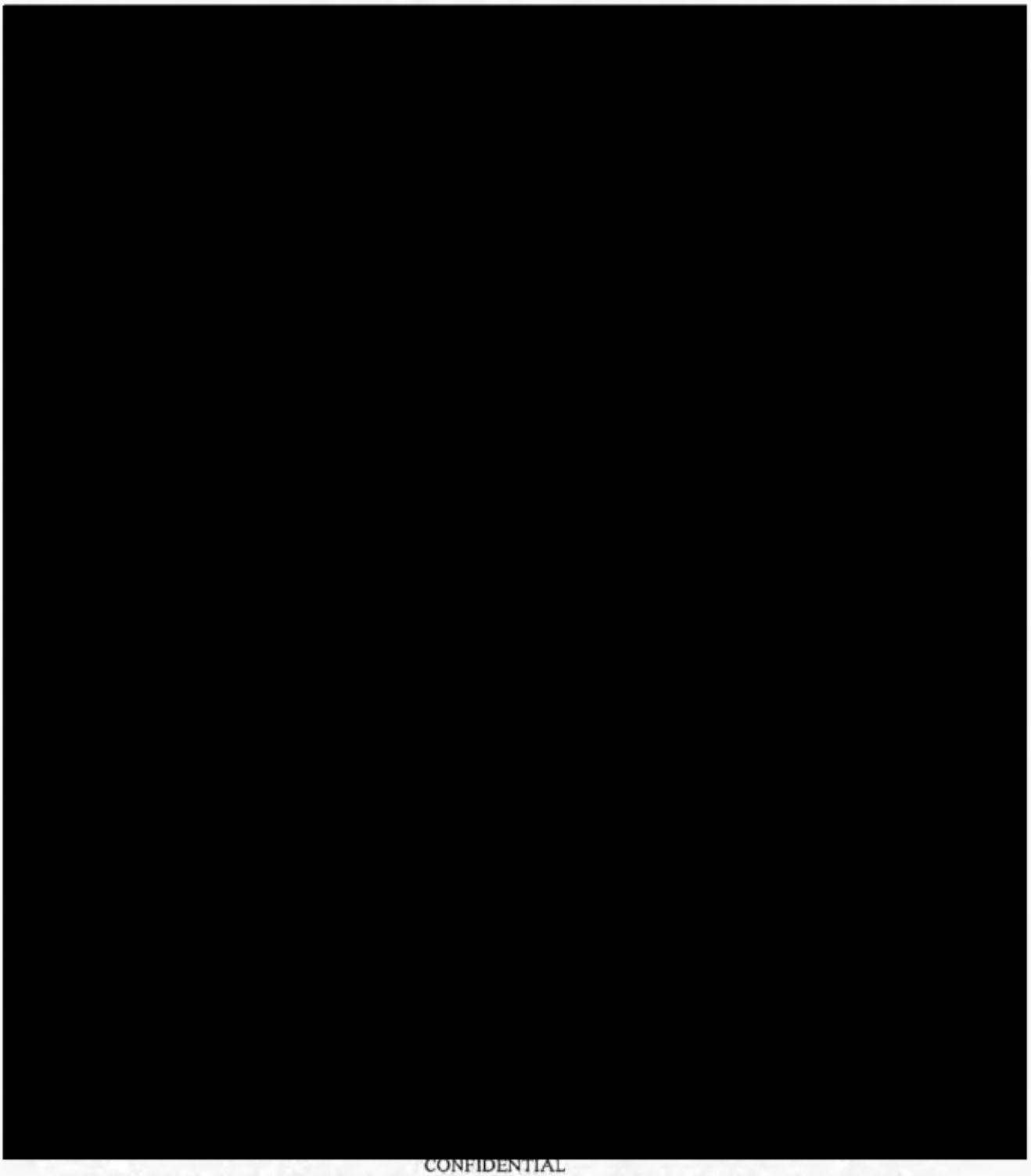
Appendix D MSTCQ: Adapted Sclerosis Treatment Concerns Questionnaire

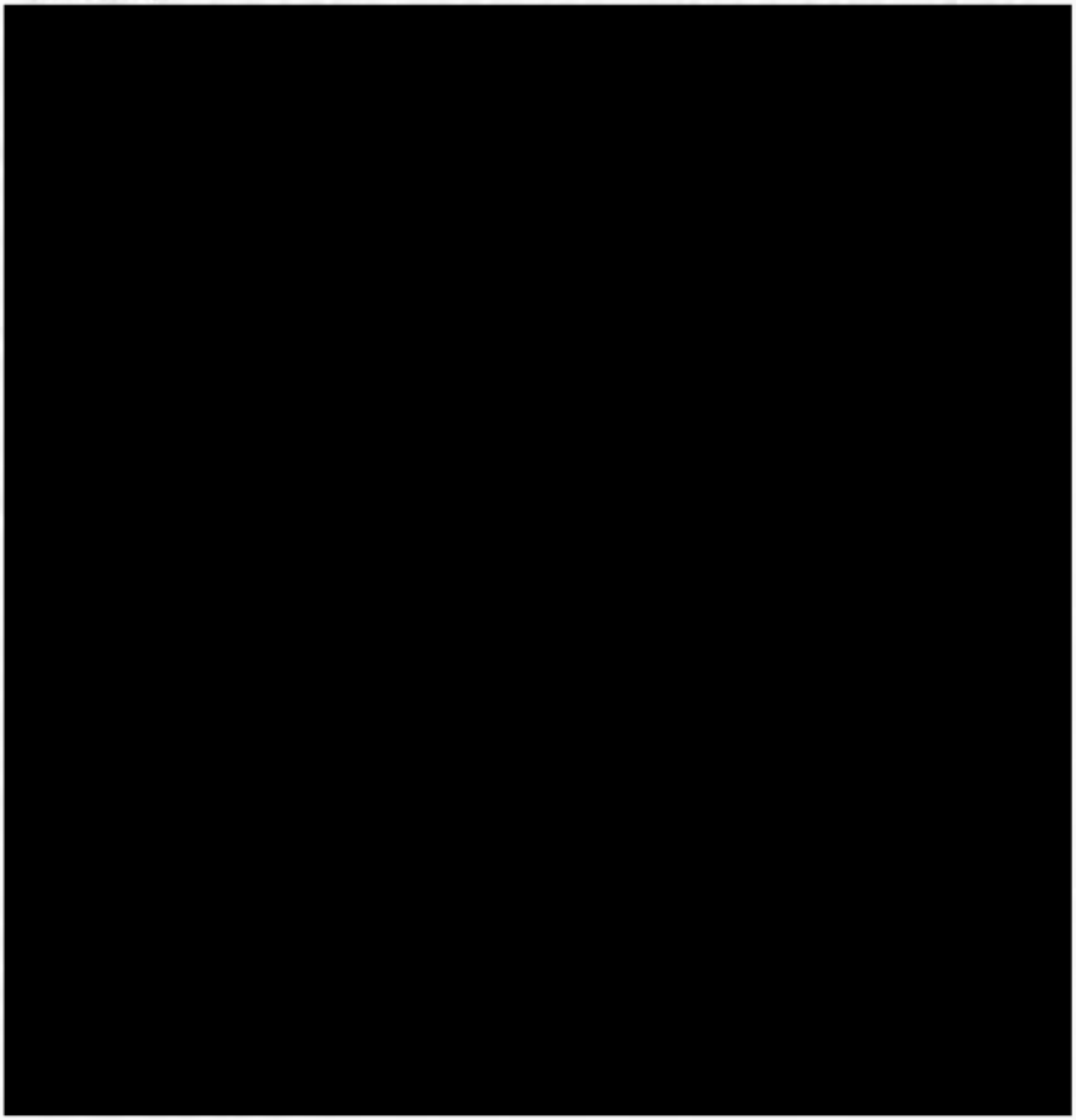
Appendix E MusiQol: Multiple Sclerosis International Quality of Life questionnaire

Appendix F FSS: Fatigue Severity Scale

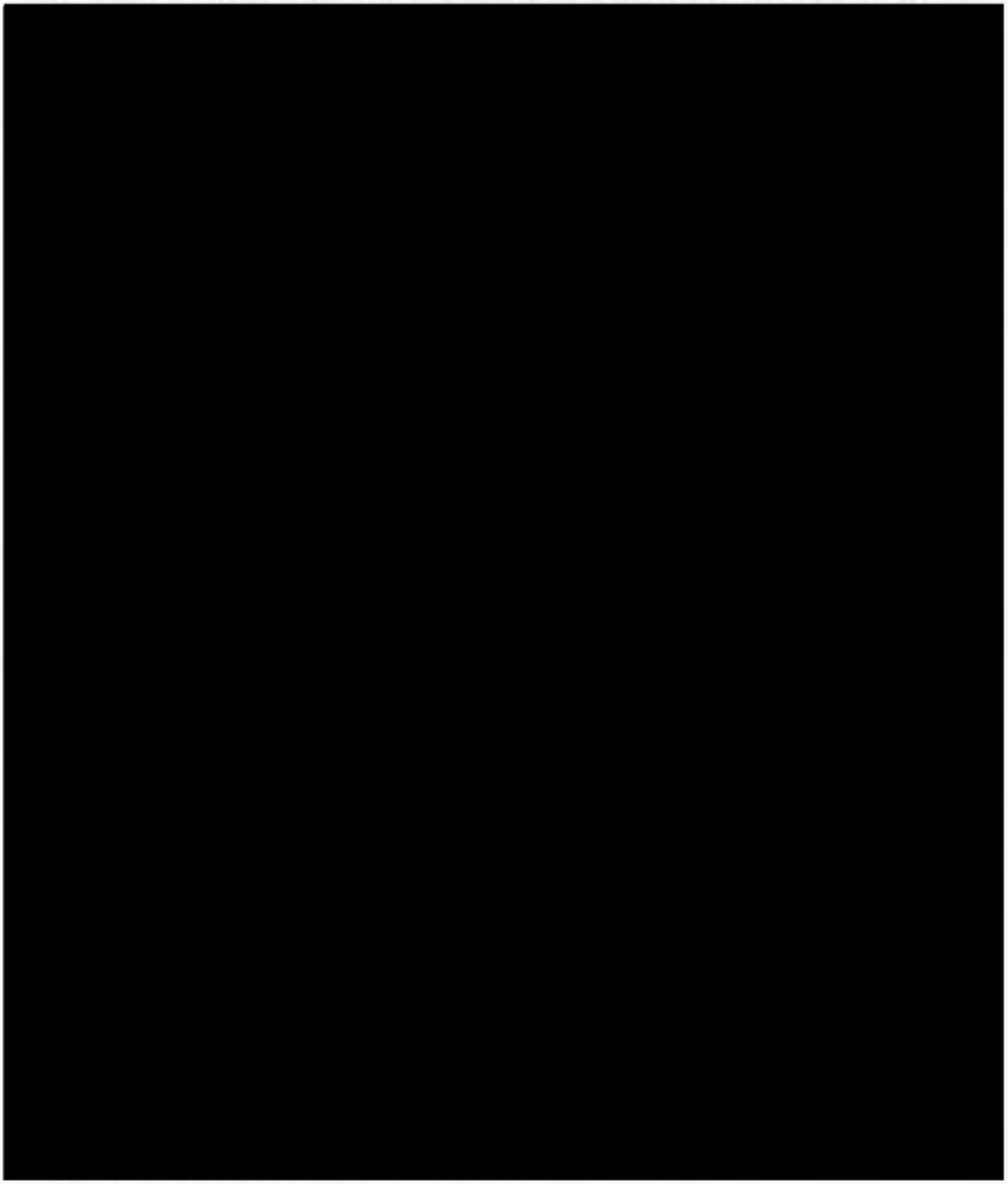
Appendix G Biogen Medically Significant Terms List

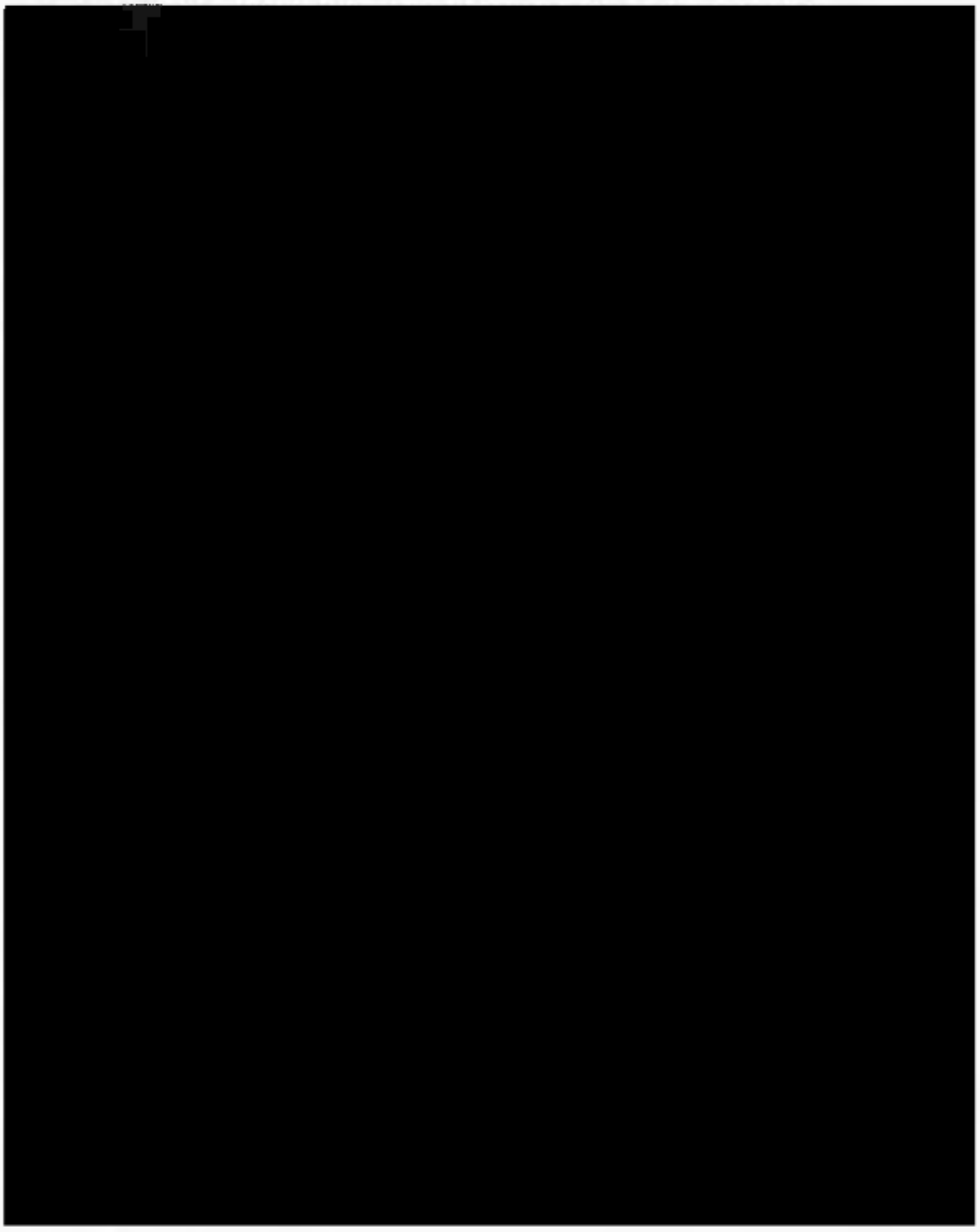
Appendix A Expanded Disability Status Score (EDSS) (Kurtzke)



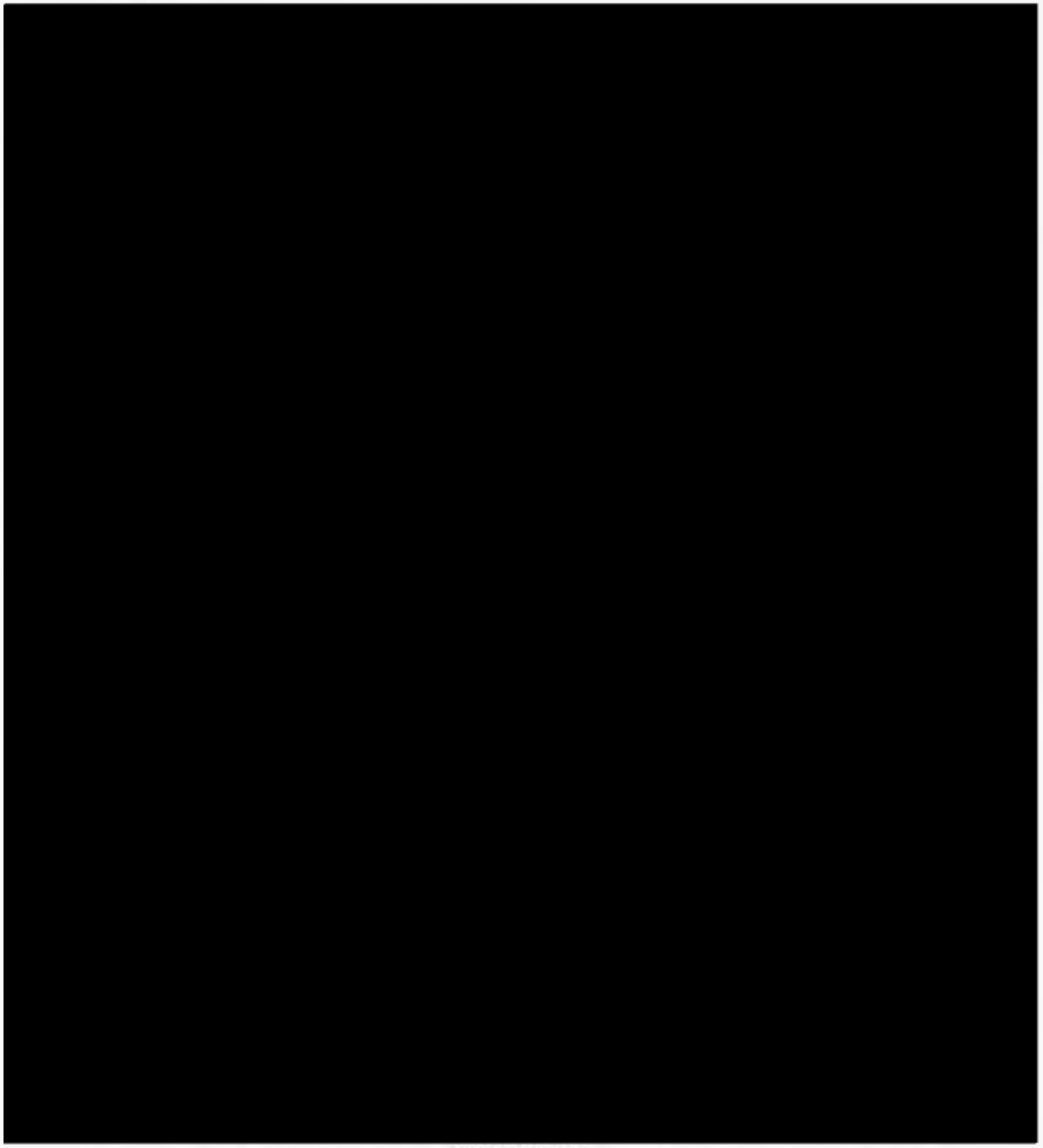


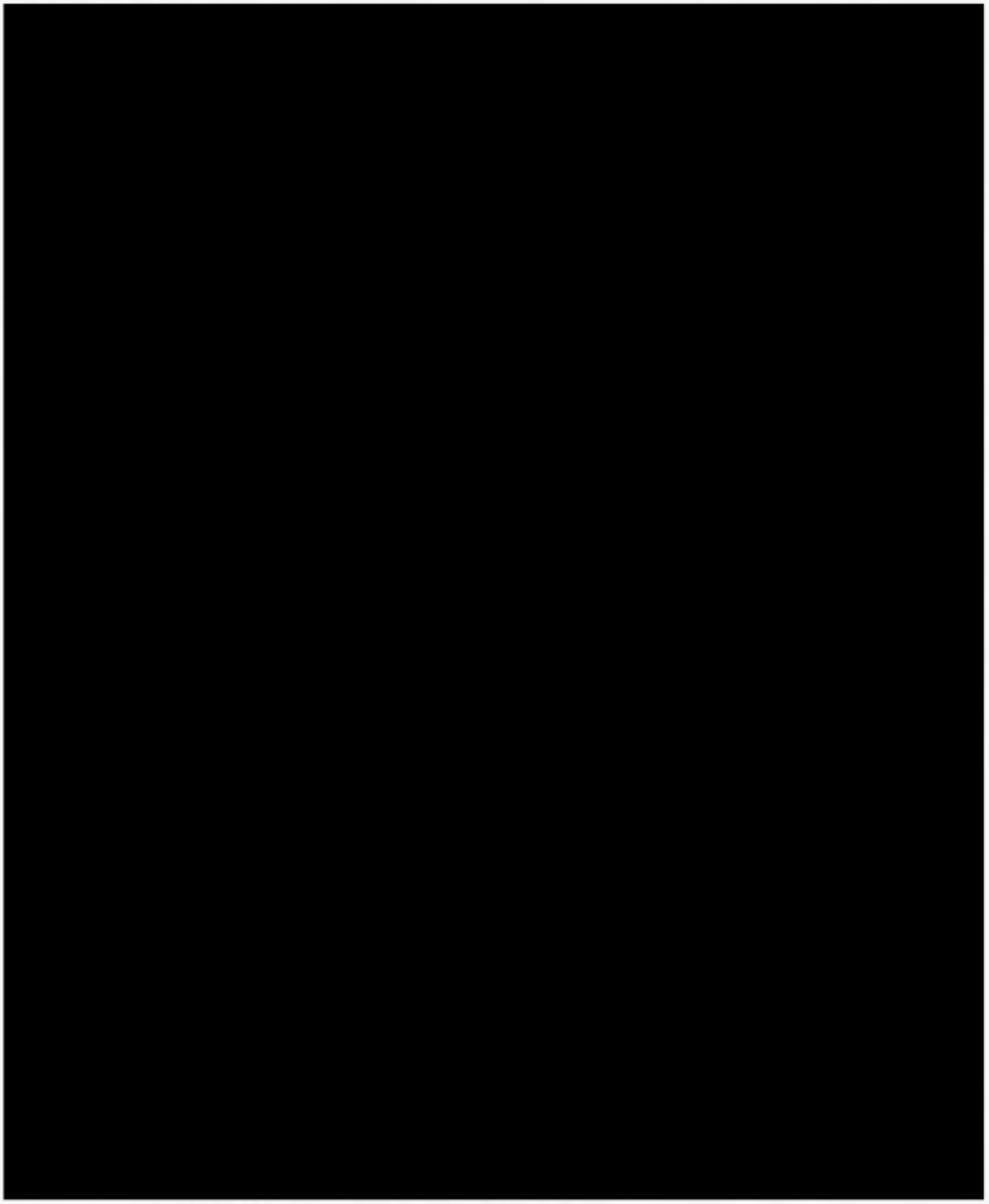
Appendix B TSQM9: Abbreviated Treatment Satisfaction Questionnaire to Medication





Appendix C Treatment Adherence Assessment





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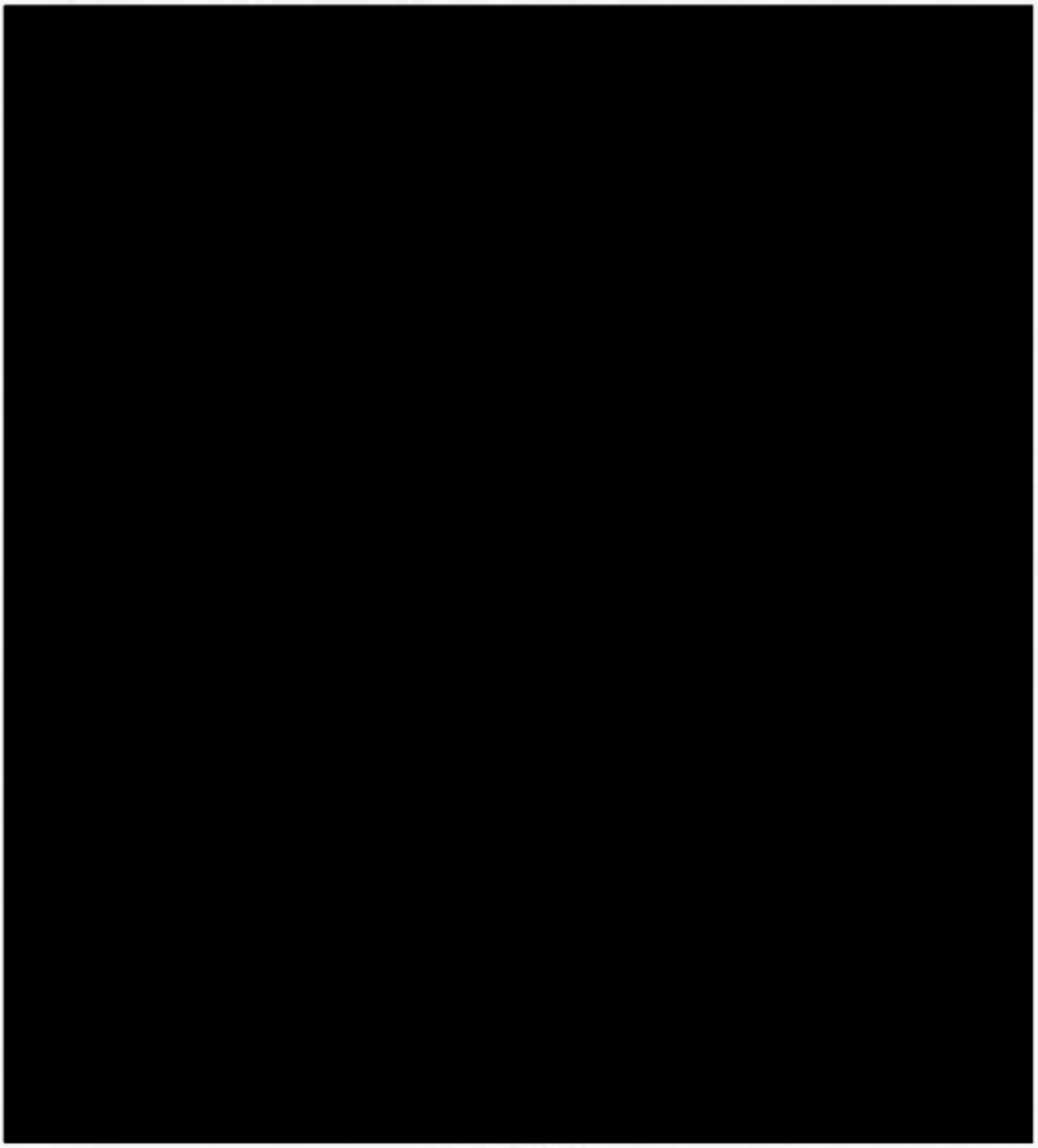
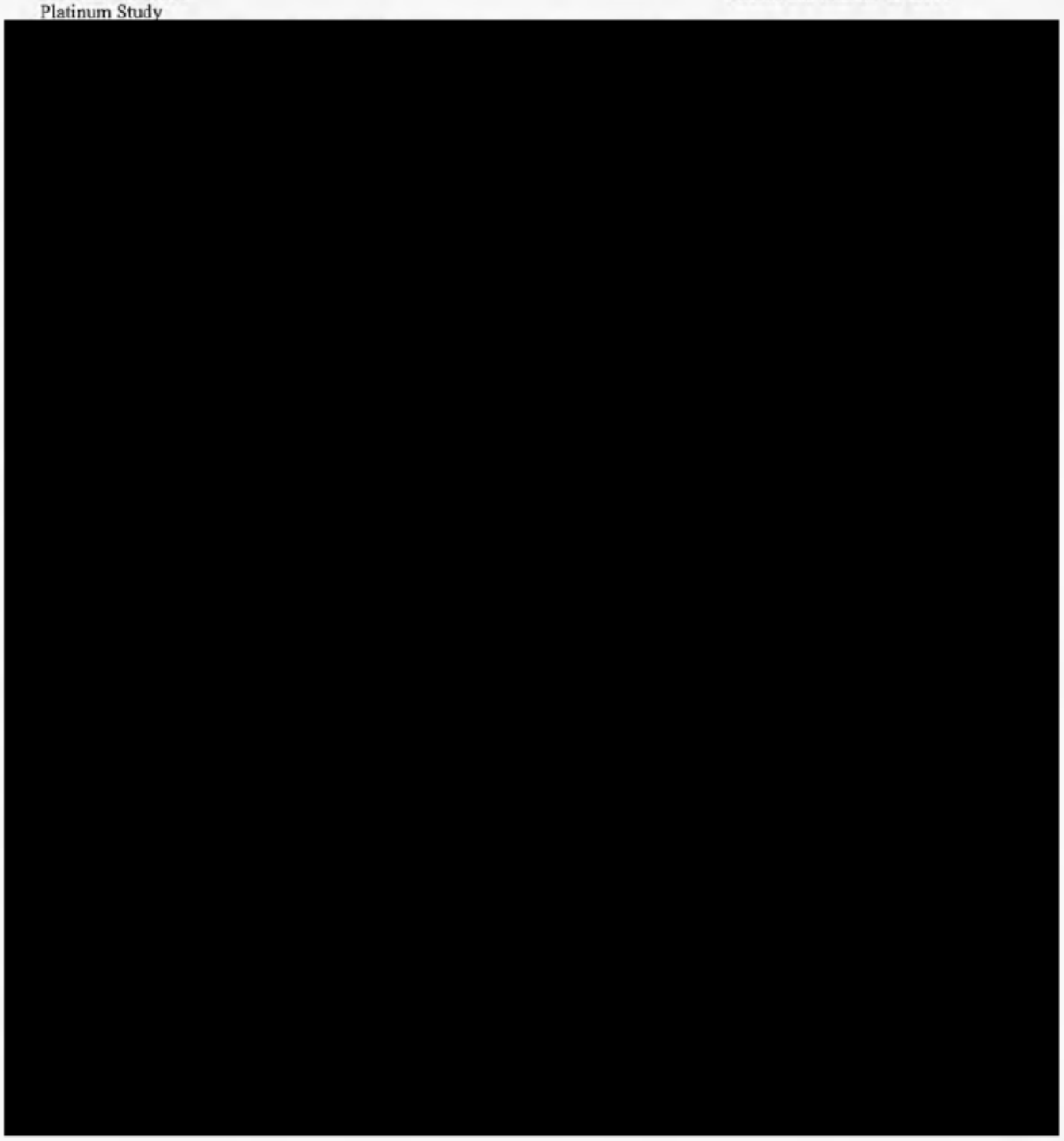
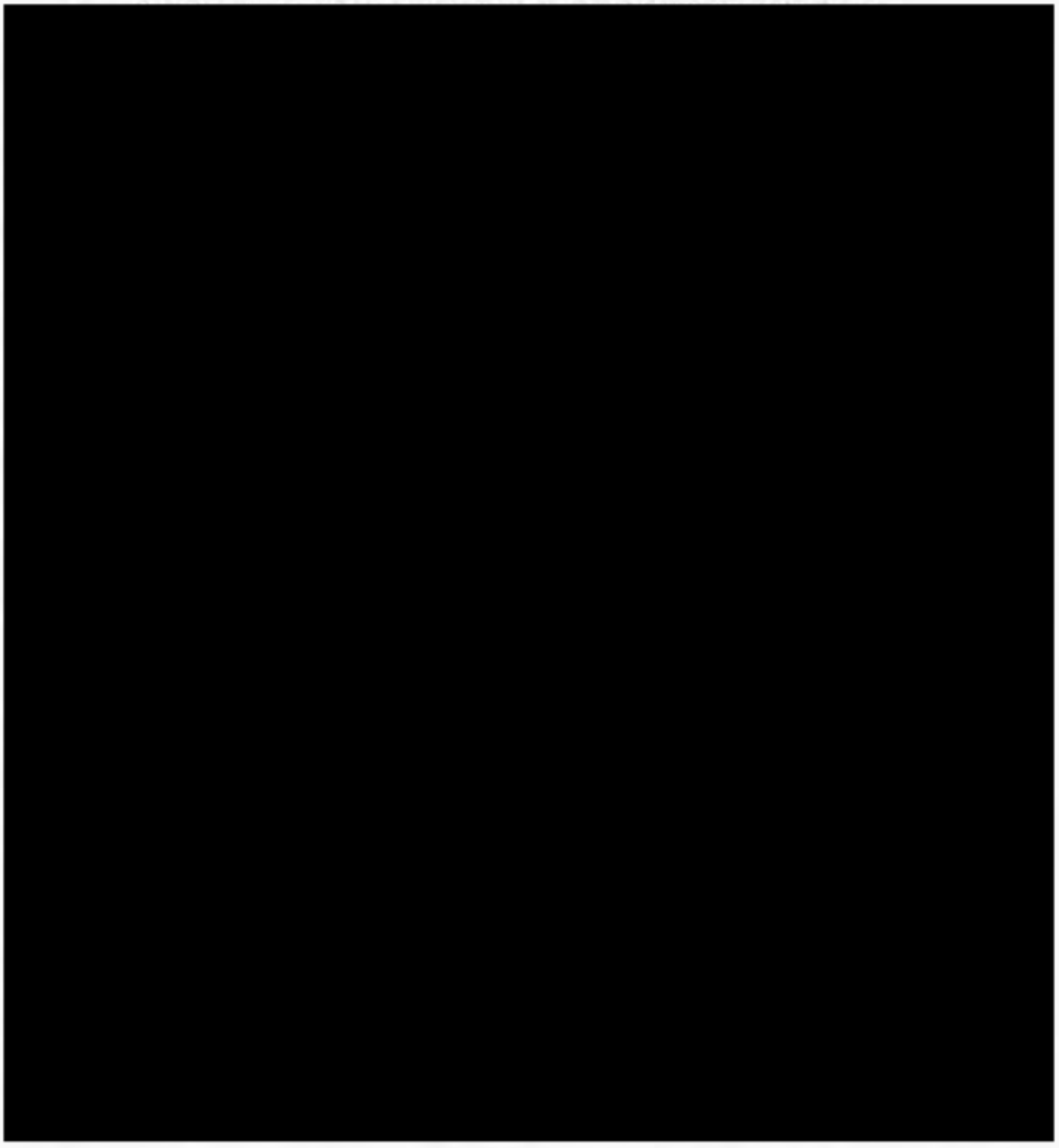
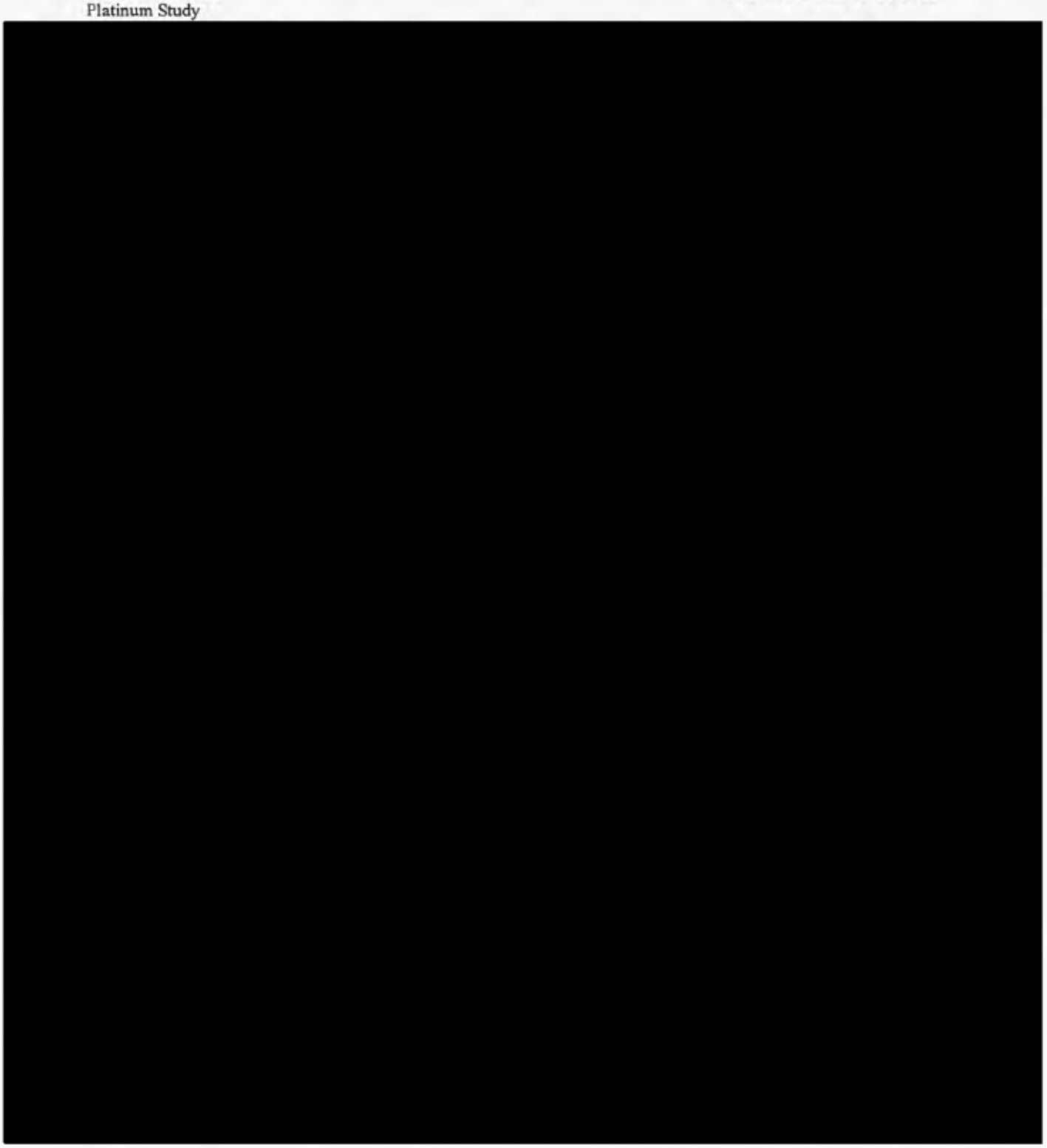
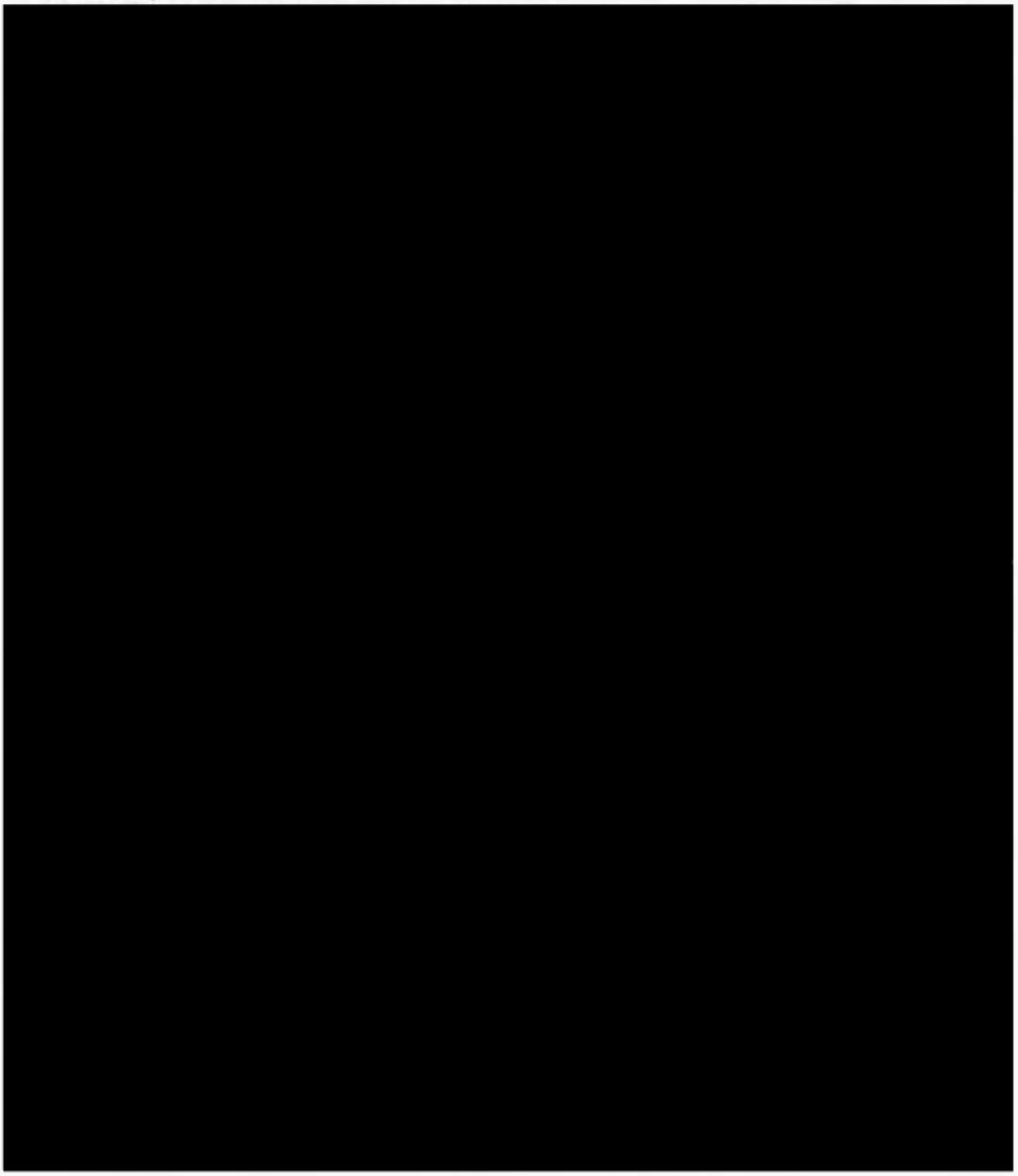
Appendix D MSTCQ: Adapted Sclerosis Treatment Concerns Questionnaire

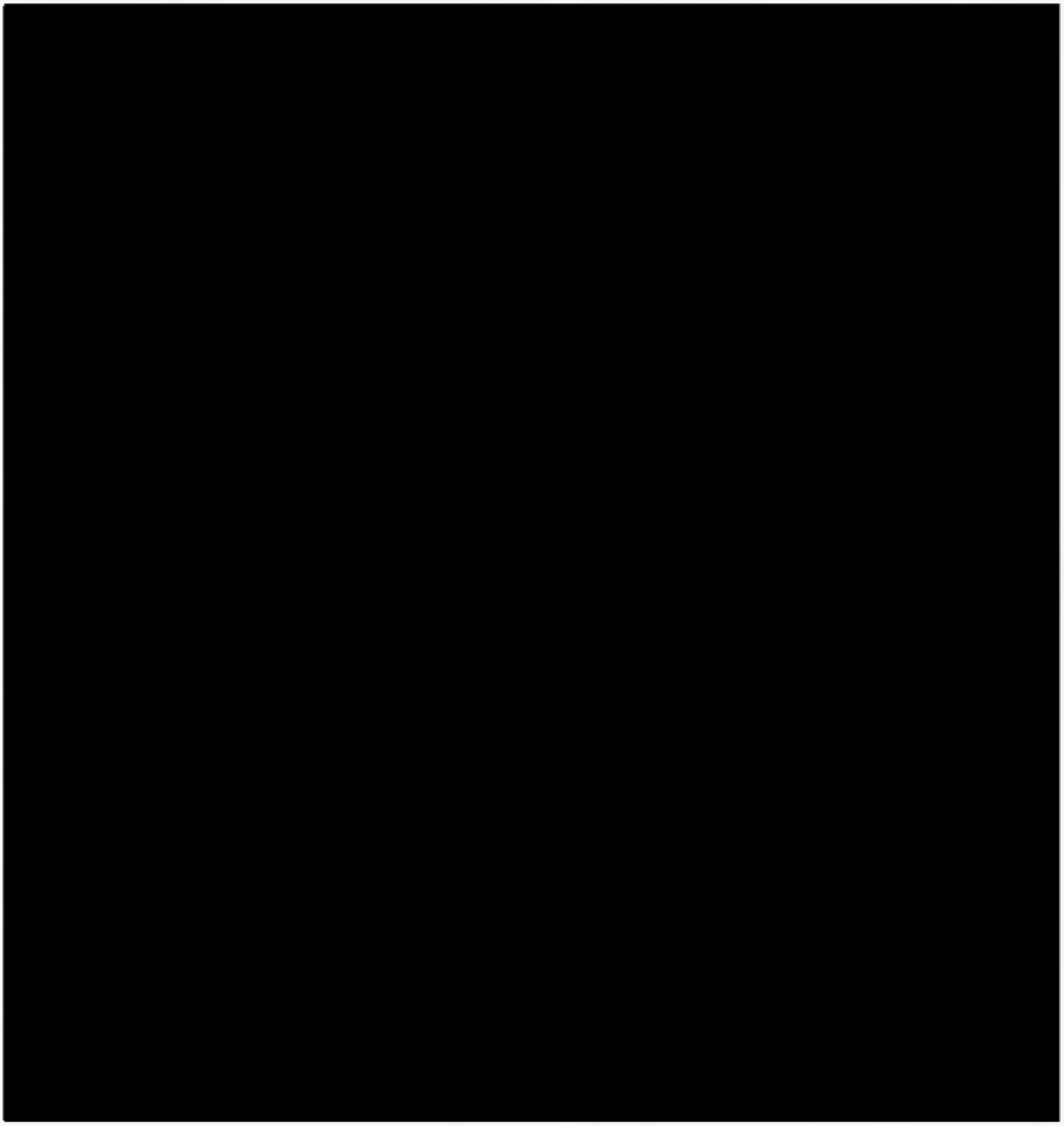


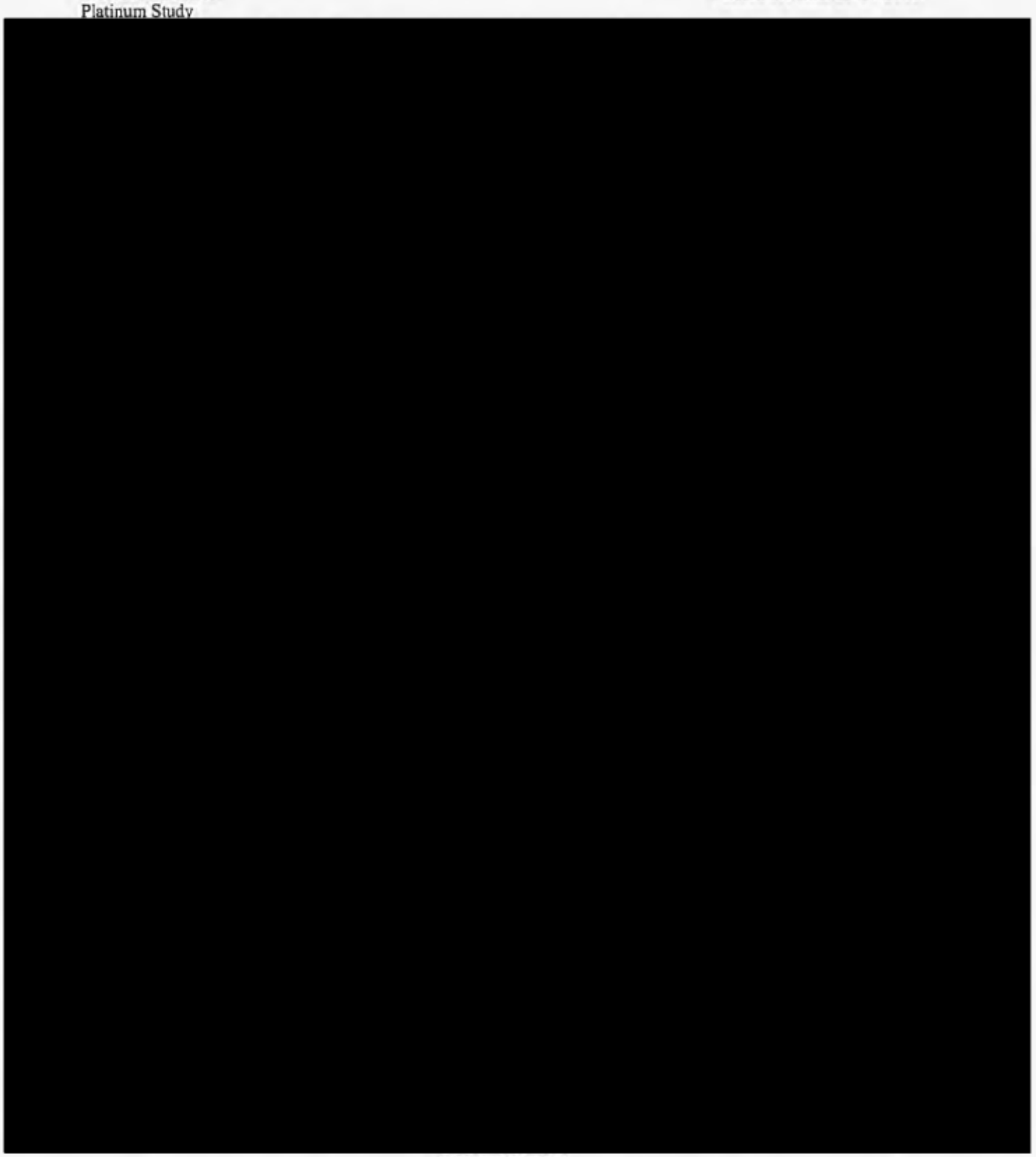




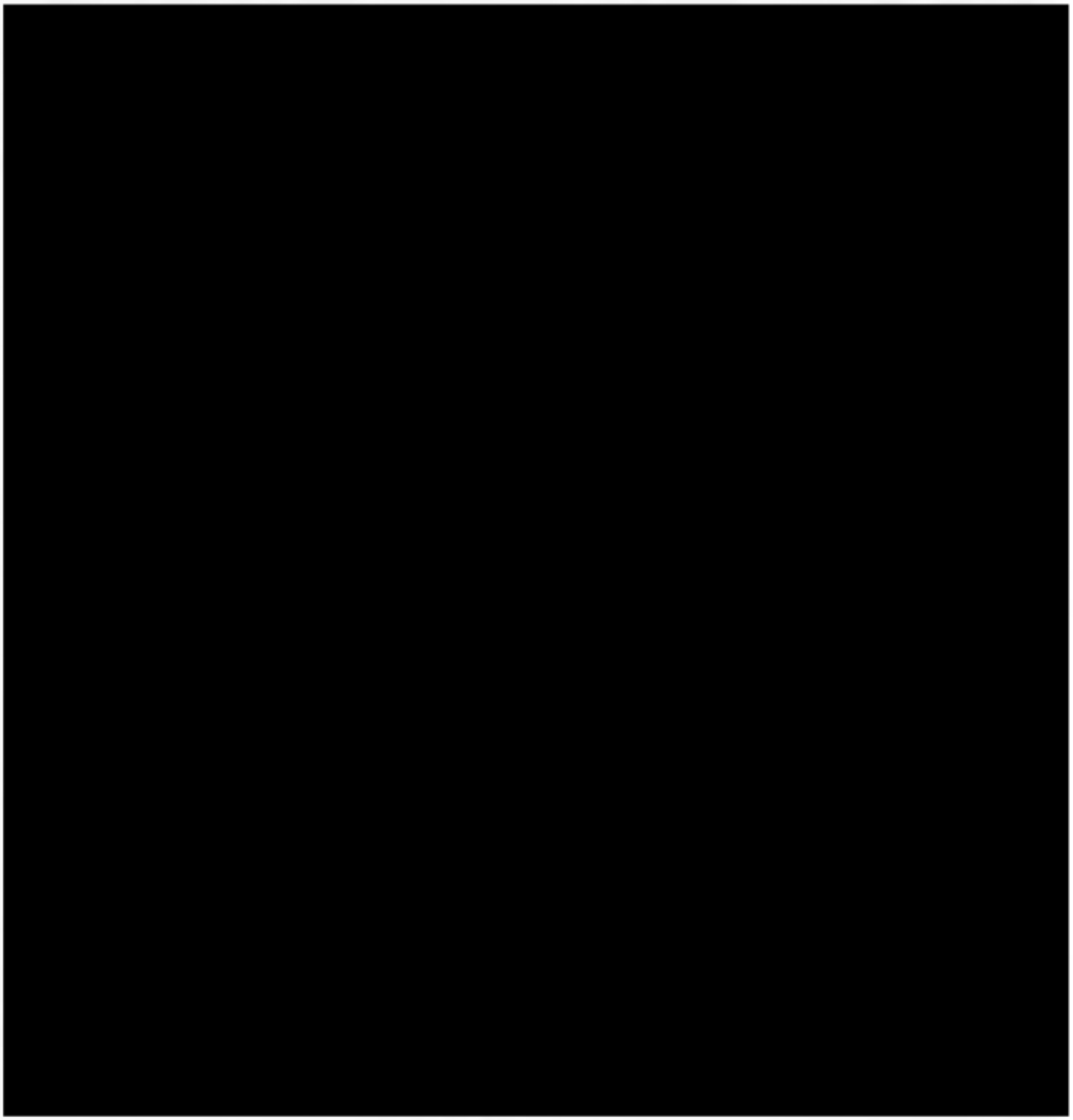


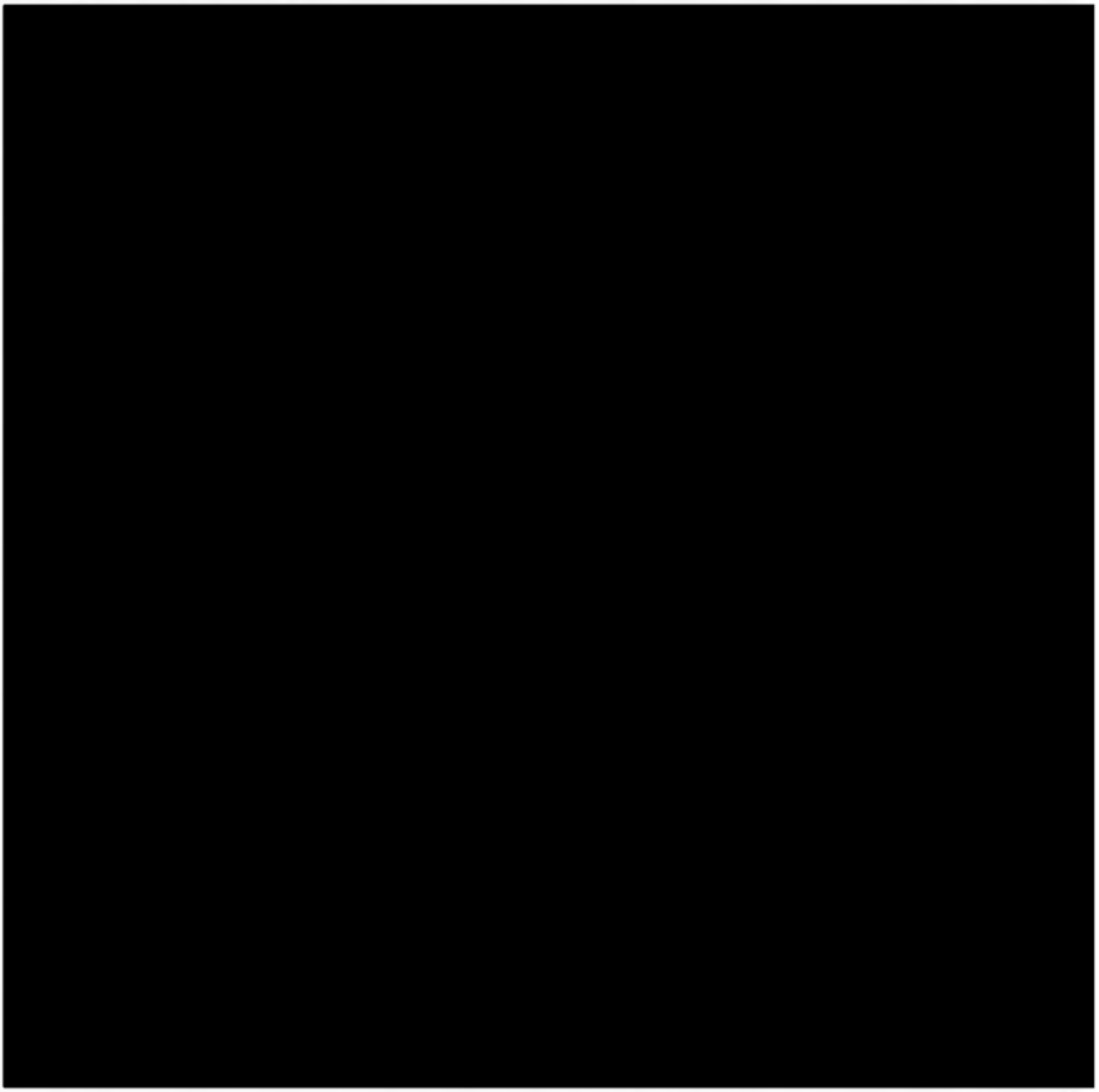






Appendix D MSTCQ: Adapted Sclerosis Treatment Concerns Questionnaire





Appendix F - FSS Fatigue Severity Scale

[redacted]

Appendix G Biogen Medically Significant Terms List

biogen idec	SABR-JA-14 v3.0 **Medically Significant List**	**Safety and Benefit-Risk Management**

1.0 PURPOSE

To describe adverse event reports always considered medically significant and therefore SERIOUS.

2.0 SCOPE

The medically significant list applies to Biogen Idec marketed products.

3.0 RESPONSIBILITIES

It is the responsibility of all SABR Safety Associates and contracted partners processing adverse events to ensure that the list of adverse events described in this job aid are considered medically significant and therefore, SERIOUS.

4.0 PROCEDURE

4.1 The following reported adverse events should be considered SERIOUS and forwarded to Biogen Idec, SABR within one business day upon receipt.

- Anaphylactic Shock
- Angioedema
- Aplastic Anemia
- Cancer –all types
- Cardiomyopathy
- Cardiomegaly
- Cirrhosis
- Congestive Heart Failure
- Convulsion/Seizure (all types)
- Hepatitis
- Heart Attack/Myocardial Infarction

biogen idec	SABR-JA-14 v3.0 Medically Significant List	Safety and Benefit-Risk Management

- Ischemic Colitis
- Pancytopenia
- Primary Biliary Cirrhosis
- Primary Pulmonary Hypertension
- Primary Sclerosing Cholangitis
- Progressive Multifocal Leukoencephalopathy (PML)
- Pulmonary Fibrosis
- Renal Failure
- Retinal Detachment
- Sarcoidosis
- Spontaneous Abortion/Miscarriage
- Stevens-Johnson Syndrome
- Stroke – (not TIA-Transient Ischemic Attack)
- Suicide Attempt
- Temperature > or = 105 degrees F or 40 55 degrees C
- Toxic Epidermal Necrolysis

4.1.1 Please contact your Biogen Idec SABR management liaison for any questions or concerns about the contents of this JA.

Signature: [redacted]

Email: [redacted]

Title: [redacted]

Company: Biogen