COVER PAGE

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Study Protocol

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An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity (Study OS3440-3005).

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CLINICAL STUDY PROTOCOL

Title Page

Protocol Title:	An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity (Study OS440-3005)
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Signature Page

Title: An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity (Study OS440-3005)

CONFIDENTIAL

Document Number: CLN.OS440-3005.PR.A02.USA

Investigator Protocol Agreement

Title: An Open-Label Study to Evaluate the Long-Term Safety of Arbaclofen Extended-Release Tablets in Multiple Sclerosis Patients with Spasticity (Study OS440-3005)

CONFIDENTIAL

Document Number: CLN.OS440-3005.PR.A02.USA

By my signature, I confirm that my staff and I have carefully read and understand this protocol or protocol amendment, and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by Osmotica Pharmaceutical or its designee. For protocol amendments, I agree not to implement the amendment without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB), the Independent Ethics Committee (IEC), or their equivalent, and regulatory authority, except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

_____ _____

Investigator's Signature **Date**

Name: _____

Address: _____

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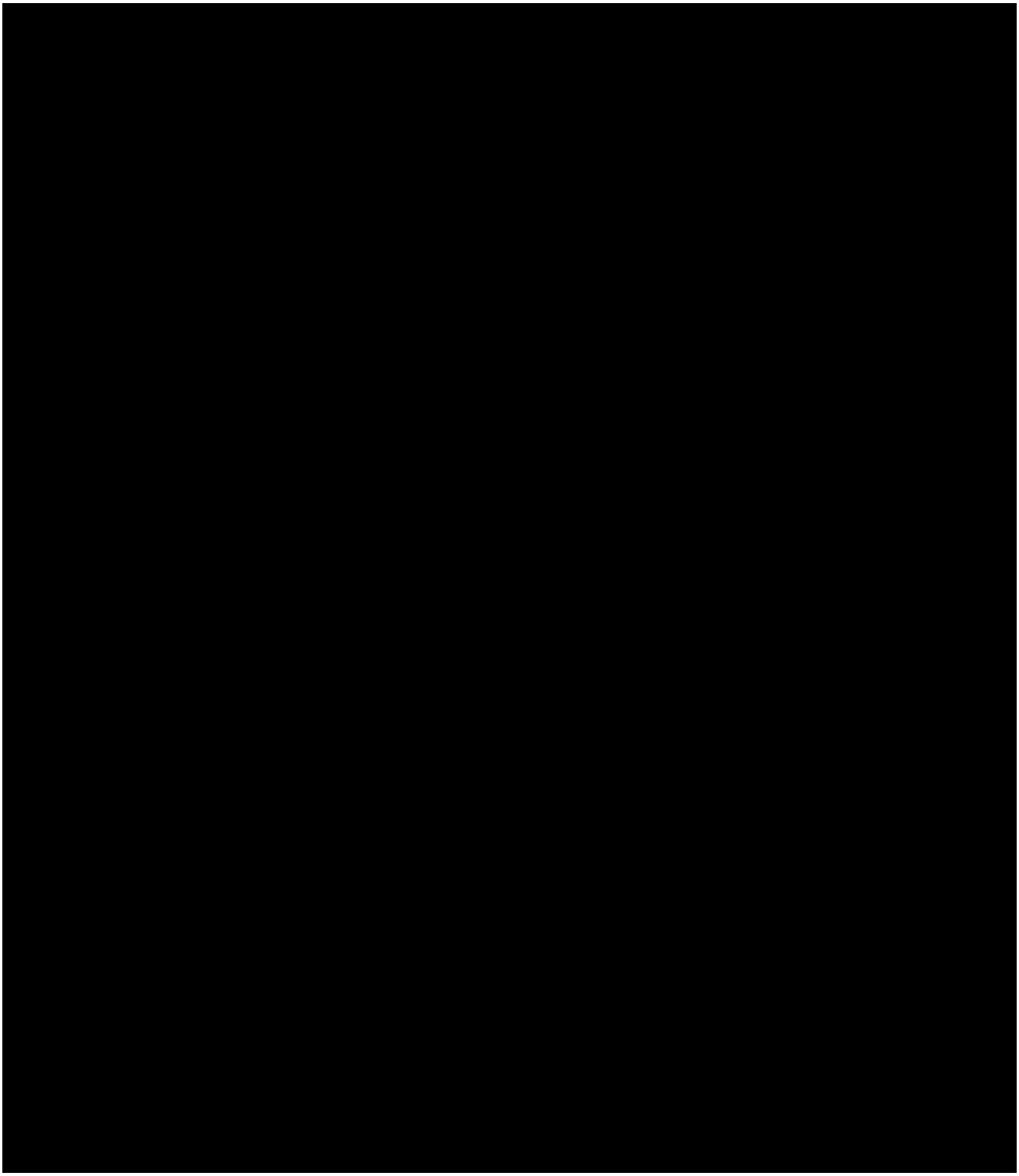
List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AERT	Arbaclofen extended-release tablets
ALT	Alanine transaminase
AST	Aspartate transaminase
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CNS	Central nervous system
CRO	Contract Research Organization
C-SSRS	Columbia–Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
DSS	Disability Status Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
FS	Functional system
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LUTS	Lower urinary tract symptoms
mAS	Modified Ashworth Scale
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple sclerosis
NARCOMS	North American Research Committee on MS
NIMH	National Institute of Mental Health
PGIC	Patient Global Impression of Change
PT	Preferred term
RBC	Red blood cell
RDC	Remote data capture
ROM	Range of movement
RR	Relapsing-remitting (MS)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SP	Secondary-progressive (MS)
TEAE	Treatment-emergent adverse event
TNmAS-MAL	Total Numeric-transformed mAS score of the most affected limb
US	United States
USP	Urinary Symptom Profile – USP© questionnaire
WBC	White blood cell
WHO	World Health Organization

1 STUDY ADMINISTRATIVE STRUCTURE



2 INTRODUCTION

2.1 Multiple Sclerosis and Spasticity

Multiple sclerosis (MS) is an acquired inflammatory demyelinating disease of the central nervous system (CNS) that is regarded as the foremost cause of non-traumatic neurologic disability in adults in North America. Multiple sclerosis has a prevalence of approximately 1 case per 1,000 in the population and a predominance in women (female to male ratio, 2:1). The mean age at onset is 30 years. Although MS is a heterogeneous illness, in 85% of patients it begins with episodic, largely reversible neurologic dysfunction, in a pattern termed relapsing-remitting (RR) MS. In 75% of those patients, the disease advances over time to a steady, irreversible worsening state designated secondary-progressive (SP) MS. Less than 5% of patients have very severe disability (fulminant MS) within the first 5 years after onset, and 10% to 20% of patients remain unimpaired without therapy (benign MS) for 20 years or so.

Clinical manifestations of MS include visual loss, paresthesias, weakness, spasticity, fatigue, and pain. Multiple sclerosis symptoms may initially wax and wane with the onset and resolution of exacerbations. However, in the latter disease stages, most patients progress to have some permanent disability. Multiple sclerosis treatment relies on pharmaceutical agents to slow disease progression and reduce the burden of MS symptoms.

Spasticity is a common complication in MS and occurs in up to 84% of patients. The main sign of spasticity is resistance to passive limb movement characterized by increased resistance to stretching, clonus, and exaggerated deep reflexes. The associated features of spasticity, including pain, gait disorders, fatigue, and loss of function, significantly affect patient quality of life. Data collected from the North American Research Committee on MS (NARCOMS) Patient Registry showed that 34% of over 20,000 MS patients surveyed experienced moderate, severe, or total limitation of physical abilities due to spasticity. Consequently, one of the main objectives for the functional management of MS is the symptomatic treatment of spasticity, aiming to improve gait, hygiene, and all the impeded activities of daily living. However, current oral pharmacologic treatments of MS fail in the total control of this problem, both for intolerability or lack of efficacy, defining the unmet medical need for treatment of spasticity.

Baclofen has been in clinical use for more than 35 years and the benefits and risks are well characterized. It is approved for the treatment of spasticity due to MS and spinal cord injury and is a first-line pharmacotherapy as described in the MS Council for Clinical Practice Guidelines for treatment of spasticity in MS. However, the therapeutic potential of baclofen is limited because it is poorly tolerated by patients due to the side effects of sedation, drowsiness, and worsening of fatigue. Therefore, an unmet medical need exists for an effective, better tolerated oral treatment of spasticity.

Baclofen is a racemate (rac-baclofen) consisting of an equal mixture of two enantiomers: the l- or R-enantiomer (arbaclofen) and the d- or S-enantiomer.

Osmotica Pharmaceutical is currently developing arbaclofen extended-release tablets (AERT) for the treatment of spasticity in patients with MS. Arbaclofen is the active R-enantiomer of baclofen and it has been postulated that the efficacy of baclofen is primarily due to the R-enantiomer. This

clinical study is an open-label extension of the Phase 3 double-blind Study OS440-3004 to evaluate the long-term safety and tolerability of AERT in patients with spasticity due to MS.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of AERT in patients with spasticity due to MS.

3.2 Secondary Objectives

The secondary objectives are to:

- Assess the Patient Global Impression of Change (PGIC) over 1 year.
- Assess the Total Numeric-transformed modified Ashworth Scale score of the most affected limb (TNmAS-MAL) over 1 year.
- Assess the Expanded Disability Status Scale (EDSS) over 1 year.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a multicenter, open-label, long-term extension study to evaluate the safety and tolerability of oral AERT in patients with spasticity due to MS. Subjects from the double-blind study (Study OSS440-3004) may rollover into this open-label extension study, as well as *de novo* subjects, provided that all inclusion and none of the exclusion criteria are met. Eligible *de novo* subjects will undergo a washout period withdrawing all medications used for anti-spasticity and/or muscle relaxation up to 21 days prior to enrolling in this open-label study. There will be a 9-day titration period, then a 52-week maintenance period, followed by a 2-week taper period. Figure 1 presents the timeline diagram for the study. Figure 2 presents the open-label dosing regimen flowchart, including titration and taper doses, to be used during the study. Once the subject has reached the maintenance dose, they will remain on that dose for approximately 1 year. The maintenance dose will be the highest tolerated dose not exceeding 80 mg per day. Table 1 presents the schedule of assessments, including study visits and weeks, for the study.

4.2 Rationale for Study Design and Dose Selection

Chronic exposure in an open-label extension design is appropriate to evaluate the safety of long-term use of an investigational product. The omission of a control group is appropriate. The subjects will be selected according to predefined entry criteria from the previous Phase 3, randomized, multicenter, double-blind, placebo-controlled study. The open-label study treatment duration of approximately 1 year is adequate for chronic exposure. Nonclinical arbaclofen data from a 3-month rat toxicity study (Study 0460RO24.001) show margins of exposure greater than 1 and adverse effects at exposures up to 10-fold higher than those projected to occur in this Phase 3 study that were not life-threatening, were clinically monitorable, and were reversible, which

supports a dose level of 80 mg. To date, Osmotica has conducted 11 clinical studies (Phases 1 through 3) utilizing AERT in doses up to 80 mg/day in single and divided doses.

The open-label extension study is necessary to obtain safety information about the long-term use of AERT at the highest target dose to treat patients with spasticity due to MS because it is a chronic condition.

5 STUDY POPULATION

It is anticipated that approximately 50% of subjects randomized into the double-blind study (Study OSS440-3004) may rollover into this open-label study. In addition, United States (US) subjects who did not participate in Study OS440-3004 (i.e., *de novo* subjects) may also enroll into the current study provided that all inclusion and none of the exclusion criteria are met. In total, approximately 300 subjects are to be enrolled in order to achieve treatment of at least 100 subjects for 6 months, and 50 subjects at 80 mg/day for at least 1 year; however, the sponsor reserves the right to end this clinical study after a sufficient number of subjects have enrolled to complete the requirement.

5.1 Inclusion Criteria

Male and female subjects will be considered eligible for participation in the study if all the following inclusion criteria are satisfied at Visit 1 (Baseline).

1. Subjects 18 to 65 years of age, inclusive.

2. An established diagnosis per McDonald Criteria (Polman et al 2011) of MS (either RR or SP course) that manifests a documented history of spasticity for at least 6 months prior to Baseline.

3. Has participated in Study OS440-3004 or is a new US subject (i.e., a *de novo* subject) who fulfills the inclusion/exclusion criteria.

    a. *De novo* subjects being considered for enrollment must have spasticity due to MS as shown by a TNmAS-MAL score ≥2[a] (Appendix 1)

4. Is willing to continue on open-label treatment with AERT as described in this protocol.

5. If receiving disease-modifying medications (e.g., interferons approved for MS, glatiramer acetate, natalizumab, fingolimod, or mitoxantrone), there must be no change in dose for at least 3 months prior to Baseline, and the subject must be willing to maintain this treatment dose for the duration of the study. If receiving AMPYRA® (dalfampridine, fampridine, 4-amino puridine), subject must be at a stable dose for at least 3 months prior to Baseline.

6. Stable regimen for at least 1 month prior to Baseline for all medications and non-pharmacological therapies that are intended to alleviate spasticity.

[a] Total numerical score of a limb accounts for the sum of the 3 main joint muscular group scores.

a. *De novo* subjects being considered for enrollment and taking medications indicated for the treatment of spasticity (i.e., baclofen, benzodiazepines, cannabinoids, carisoprodol, dantrolene, tizanidine, cyclobenzaprine, any neuroleptic, ropinoprole, tolperisone, and clonidine) must wash out from these medications for at most 21 days by Baseline in order to be eligible for study treatment. *De novo* subjects found not to meet this criterion will be withdrawn from the study and will be considered screen failures.

7. Absence of infections, peripheral vascular disease, painful contractures, advanced arthritis, or other conditions that hinder evaluation of joint movement.

8. Creatinine clearance, as calculated by the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease Study (MDRD) formula,[b] of >50 mL/minute.

9. Use of a medically highly effective form of birth control (see Section 7.8) during the study and for 3 months thereafter for women of child-bearing potential (including female subjects).

10. Willing to sign the informed consent form (ICF).

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will not qualify for the study.

1. Any concomitant disease or disorder that has symptoms of spasticity or that may influence the subject's level of spasticity.

2. Inability to rate their level of spasticity or distinguish it from other MS symptoms.

3. Use of high dose oral or intravenous methylprednisolone, or equivalent, within 3 months before Baseline.

4. History of allergy to baclofen or any inactive components of the test formulation.

5. Concomitant use of medications that would potentially interfere with the actions of the study medication or outcome variables (Appendix 5).

6. Pregnancy, lactation, or planned pregnancy during the course of the study and for 3 months after the final study visit.

7. Recent history (within past 12 months) of any unstable psychiatric disease (or yes response to questions 1 or 2 on the Columbia Suicide Severity Rating Scale [C-SSRS] at baseline), or current signs and symptoms of significant medical disorders such as severe, progressive,

[b] GFR Calculator:
GFR (mL/min/1.73 m^2) = 175 x (Scr (mg/dL))-1.154 x (Age (years))-0.203 x (0.742 if female) x (1.212 if African American) (conventional units)
GFR (mL/min/1.73 m^2) = 175 x (Scr (µmol/L)/88.4)-1.154 x (Age (years))-0.203 x (0.742 if female) x (1.212 if African American) (SI units)

or uncontrolled pulmonary, cardiac, gastrointestinal, hepatic, renal, genitourinary, hematological, endocrine, immunologic, or neurological disease.

8. History of epilepsy.

9. Current significant cognitive deficit, severe or untreated anxiety, severe or untreated depression.

10. Subjects with abnormal micturition that requires indwelling or intermittent catheterization or with lower urinary tract symptoms (LUTS) that result in a score >26 in the Baseline Urinary Symptom Profile – USP© (USP) questionnaire (Appendix 6). Subjects who are proficient in self-catheterization may be included in the study at the investigator's discretion.

11. Current malignancy or history of malignancy that has not been in remission for more than 5 years, except effectively treated basal cell skin carcinoma.

12. Subject has clinically significant abnormal laboratory values, in the opinion of the investigator at Screening (at Visit 6 for rollover subjects).

13. Any other significant disease, disorder, or significant laboratory finding, including clinically significant abnormal laboratory values or ongoing serious adverse events (SAEs) at Visit 6 (Final Visit) of Study OS440-3004, which, in the opinion of the investigator, puts the subject at risk because of participation, influences the result of the study, or affects the subject's ability to participate.

14. Planned elective surgery or other procedures requiring general anesthesia during the course of the study.

15. History of any illicit substance abuse (e.g., alcohol, marijuana, cocaine) or prescription for long-acting opioids within the past 12 months (tramadol use will be allowed).

16. Participation in another clinical research study (with the exception of Study OS440-3004) within 1 month of Baseline.

6 STUDY PROCEDURES

Table 1 and the following subsections present the planned study visits, timing, and details for study procedures. Figure 1 presents the timeline diagram for the study. The flowchart depicting the open-label dosing schema for this study is presented in Figure 2.

Table 1: Schedule of Assessments, Study OS440-3005

Assessment or Procedure	Screening[1]	Baseline[1]	Baseline[1]	Visits							Final Visit[2]
Study Visit	***De Novo* subjects only**	***De Novo* subjects only**	**(V6 of prior DB Study)**	**1**	**2**	**3**	**4**	**5**	**6[6]**	**7 (telephone visit)**	**8**
Study Week	**up to 21 days before Baseline**	**0 (±3 days)**	**0 (±3 days)**	**2 (±3 days)**	**6 (±5 days)**	**14 (±5 days)**	**28 (±5 days)**	**42 (±5 days)**	**54 (±3 days)**	**56 (±5 days)**	**60 (±3 days)**
Written informed consent	X		X								
Inclusion and exclusion criteria	X		X								
Withdrawal anti-spasticity medication	X		X								
Assign enrollment number		X	X								
Demography	X		X								
Medical/surgical history; physical examination; height	X		X								
Weight	X		X				X				X
Vital signs[3]	X	X	X	X	X	X	X	X	X		X
Hematology/serum chemistry/urinalysis	X		X		X	X	X	X	X		X
Electrocardiogram	X		X				X				X
Pregnancy test[4]	X	X	X	X	X	X	X	X	X		X
C-SSRS	X	X	X	X	X	X	X	X	X		X
TNmAS-MAL[5]	X	X	X				X				X
EDSS	X		X				X				X
PGIC		X	X								X
USP© questionnaire	X	X	X	X	X	X	X	X	X		X
Dispense study medication		X	X	X	X	X	X	X	X[6]		
Collect unused study medication				X	X	X	X	X	X		X
Adverse event assessment		X	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X
Schedule/confirm next study visit		X	X	X	X	X	X	X	X	X	

C-SSRS = Columbia–Suicide Severity Rating Scale; DB = double-blind; EDSS = Expanded Disability Status Scale; FV = final visit; PGIC = Patient Global Impression of Change; TNmAS-MAL = Total Numeric-transformed modified Ashworth Scale score of the most affected limb; USP = Urinary Symptom Profile
(footnotes on next page)

Table 1 - Footnotes:

1. Baseline for the study will be conducted at the same time as Visit 6/Day 92 (Final Visit) of Study OS440-3004 for subjects willing to continue into this study. All assessments performed at Visit 6/Day 92 (Final Visit) of Study OS440-3004 should not be repeated but should be recorded as the same assessments at Baseline for this study.

   Note: For *de novo* subjects being considered for enrollment, a Screening visit should occur a maximum of 21 days prior to Baseline to allow for any concomitant medication wash-out required for Inclusion Criterion 6. For *de novo* subjects, only the following assessments and procedures will be performed at the Baseline visit: assign enrollment number, vital signs, urine pregnancy test, C-SSRS, TNmAS-MAL, PGIC, USP, dispensing of study medication, recording of AEs and concomitant medications, and scheduling/confirmation of the next study visit.

2. If a subject prematurely withdraws from the study, the subject should taper from study medication as described in Section 7.1 and all evaluations described under Visit 8/Week 60 (Final Visit) must be performed.

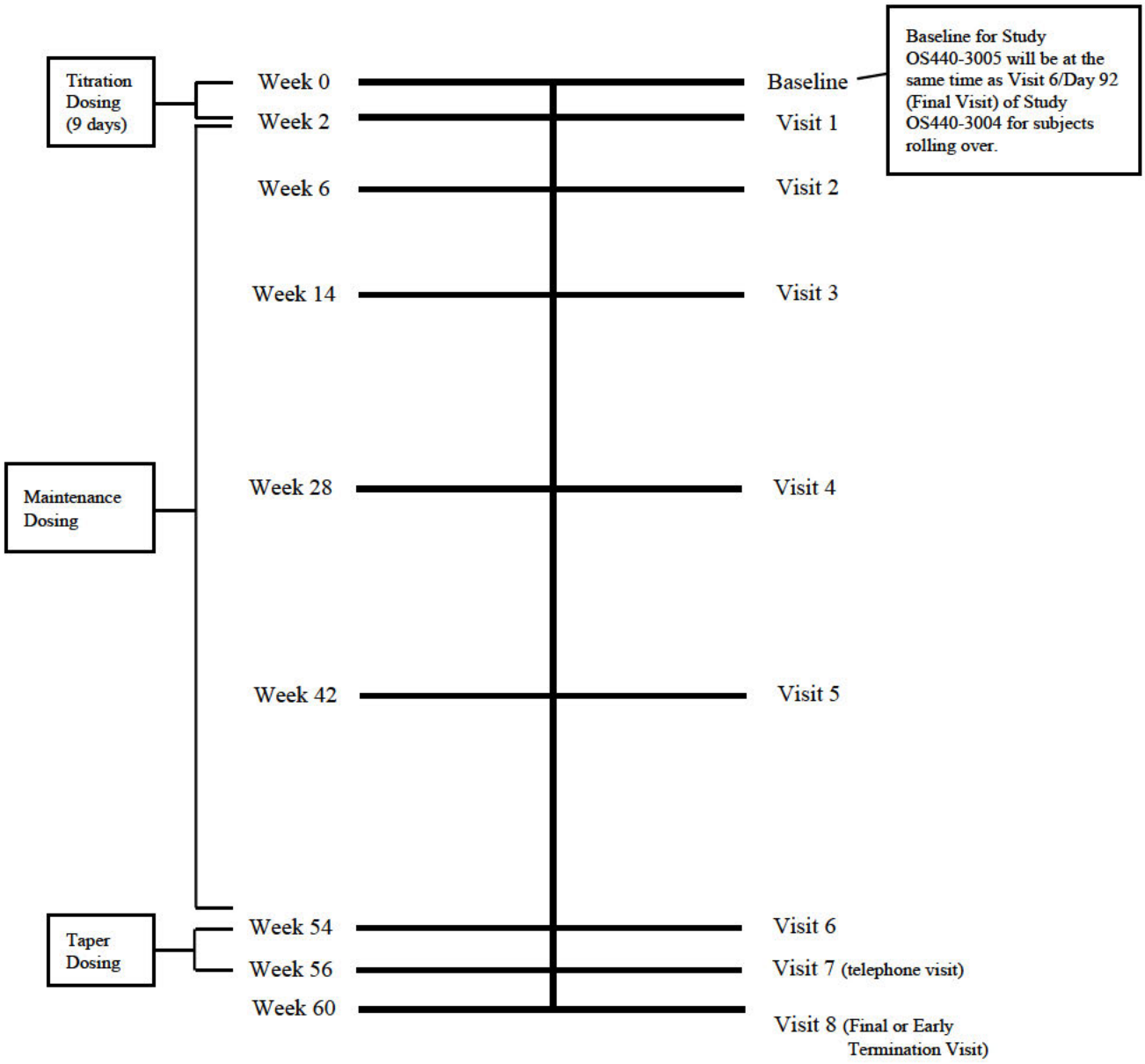
3. Vital signs will be measured with the subject in a supine position and in a standing position 3 minutes after the supine assessment is completed. Body temperature and respiratory rate will be measured only during the supine assessment.

4. For *de novo* subjects, premenopausal women of childbearing potential must have a negative serum pregnancy test within 21 days before Baseline. Urine pregnancy testing will be performed for all female subjects at the other visits as noted.

5. The TNmAS-MAL assessment will be performed prior to any scheduled laboratory draws. The most affected limb will be determined by the investigator.

6. At the end of treatment, a 2-week taper period will take place from Weeks 54 to 56. Subjects who discontinue early should also follow the 2-week taper period.

Figure 1: Timeline Diagram, Study OS440-3005



6.1 Screening – *De Novo* Subjects Only

For *de novo* subjects being considered for enrollment, a Screening visit (shown in Table 1) should occur a maximum of 21 days prior to Baseline to allow for any concomitant medication wash-out required for Inclusion Criterion 6. For d*e novo* subjects, the following procedures will be done at this Screening visit:

- Obtain a signed and dated ICF from each subject prior to any study-specific procedures being conducted (Section 13.3).
- Assess eligibility according to the inclusion (Section 5.1) and exclusion criteria (Section 5.2).
- After establishing the subject's eligibility to participate, explain to *de novo* subjects how to withdraw all anti-spasticity medication (up to a 21-day period) prior to the next visit.
- Record demographic data, including age, sex, race, and ethnicity.
- Record medical and surgical history (Section 9.1).
- Record physical examination results (Section 9.3).
- Record weight and height (Section 9.4).
- Record vital sign measurements, including blood pressure (BP), heart rate, respiratory rate, and body temperature (Section 9.2).
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis (Section 9.5). Subject should be fasting if possible.
- Perform a standard 12-lead electrocardiogram (ECG) (Section 9.6.1).
- Collect a sample to perform a serum pregnancy test (Section 7.8).
- Administer the Columbia–Suicide Severity Rating Scale (C-SSRS) (Section 9.6.3).
- Perform the TNmAS-MAL assessment (Section 8.2).
- Administer the EDSS assessment (Section 8.3).
- Administer the USP questionnaire (Section 9.6.2).
- Record all concomitant medications/therapies the subject is currently taking (Section 7.7).

6.2 Baseline – Visit 6 (Final Visit) of Study OS440-3004 (Week 0)

For *de novo* subjects, the following assessments and procedures will be performed at the Baseline visit: assign enrollment number, vital signs, urine pregnancy test, C-SSRS, TNmAS-MAL, PGIC,

USP, dispensing of study medication, recording of AEs and concomitant medications, and scheduling/confirmation of the next study visit.

For Study OS440-3004 subjects willing to continue into this study, Baseline for this study will be conducted at the same time as Visit 6/Day 92 (Final Visit) of Study OS440-3004. All assessments performed at Visit 6/Day 92 (Final Visit) of Study OS440-3004 should not be repeated but should be recorded as the same assessments at Baseline for this study.

At Baseline, the investigator will fully explain to the subject the objectives, characteristics, and procedures for the open-label study. Baseline assessments/procedures will include the following:

- Obtain a signed and dated ICF from each subject prior to any study-specific procedures being conducted (Section 13.3).
- Assess eligibility according to the inclusion (Section 5.1) and exclusion criteria (Section 5.2).
- Assignment of an enrollment number (Section 7.4).
- Record demographic data, including age, sex, race, and ethnicity.
- Record medical and surgical history (Section 9.1).
- Record physical examination results (Section 9.3).
- Record weight and height (Section 9.4).
- Record vital sign measurements, including blood pressure (BP), heart rate, respiratory rate, and body temperature (Section 9.2).
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis (Section 9.5). Subject should be fasting if possible.
- Perform a standard 12-lead electrocardiogram (ECG) (Section 9.6.1).
- Because contraception is required throughout the study for both males and females, the use of an acceptable method throughout the study will be discussed with all subjects (Section 7.8).
- Collect a urine sample for pregnancy testing for women of childbearing potential (Section 7.8).
- Administer the Columbia–Suicide Severity Rating Scale (C-SSRS) (Section 9.6.3).
- Perform the TNmAS-MAL assessment (Section 8.2).
- Administer the EDSS assessment (Section 8.3).
- Administer the PGIC questionnaire (Section 8.1).
- Administer the USP questionnaire (Section 9.6.2).

- Dispense the study medication. The investigator will explain to the subject how to take the study medication and the regimen to be followed until the next visit (Section 7.5).
- The site will administer the first daily dose of study medication to the subject.
- Record any adverse events (AEs) that have occurred (Section 9.7).
- Record all concomitant medications/therapies the subject is currently taking (Section 7.7).
- Schedule the next study visit.

6.3 Visits 1, 2, 3, 5, and 6 – Weeks 2, 6, 14, 42, and 54

Assessments/procedures will include the following:

- Record vital sign measurements, including BP, heart rate, respiratory rate, and body temperature (Section 9.2).
- At Visits 2, 3, 5, and 6, collect blood and urine samples for hematology, serum chemistry, and urinalysis (Section 9.5). Subject should be fasting if possible.
- Collect a urine sample for pregnancy testing for women of childbearing potential (Section 7.8).
- Administer the C-SSRS (Section 9.6.3).
- Administer the USP questionnaire (Section 9.6.2).
- Dispense the study medication. The investigator will explain to the subject how to take the study medication and the regimen to be followed until the next visit (Section 7.5).
- Collect unused study medication, assess compliance, and study drug accountability (Section 7.9).
- Record any AEs that have occurred (Section 9.7).
- Record all concomitant medications/therapies the subject is currently taking (Section 7.7).
- Schedule the next study visit.

6.4 Visit 4 – Week 28

Assessments/procedures will include the following:

- Record weight (Section 9.4).

- Record vital sign measurements, including BP, heart rate, respiratory rate, and body temperature (Section 9.2).
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis (Section 9.5). Subject should be fasting if possible.
- Perform a standard 12-lead ECG (Section 9.6.1).
- Collect a urine sample for pregnancy testing for women of childbearing potential (Section 7.8).
- Administer the C-SSRS (Section 9.6.3).
- Perform the TNmAS-MAL assessment (Section 8.2).
- Administer the EDSS assessment (Section 8.3).
- Administer the USP questionnaire (Section 9.6.2).
- Dispense the study medication. The investigator will explain to the subject how to take the study medication and the regimen to be followed until the next visit (Section 7.5).
- Collect unused study medication, assess compliance, and study drug accountability (Section 7.9).
- Record any AEs that have occurred (Section 9.7).
- Record all concomitant medications/therapies the subject is currently taking (Section 7.7).
- Schedule the next study visit.

6.5 Visit 7 End of Taper (Telephone Visit) – Week 56

- Record any AEs that have occurred (Section 9.7).
- Record all concomitant medications/therapies the subject is currently taking (Section 7.7).
- Schedule the final study visit.

6.6 Visit 8 (Final Visit or Early Termination) – Week 60

The assessments/procedures listed for Visit 8 (Final Visit) are to be completed by all subjects regardless of whether they complete the entire study or prematurely withdraw from the study. If the Final Visit is performed before Week 60 due to early termination of the subject, every effort should be made to perform the clinical evaluations as follows, especially blood sampling for hematology and serum chemistry, urinalysis, ECG, and the 2-week study drug taper. Assessments/procedures will include the following:

- Record weight (Section 9.4).

- Record vital sign measurements, including BP, heart rate, respiratory rate, and body temperature (Section 9.2).
- Collect blood and urine samples for hematology, serum chemistry, and urinalysis (Section 9.5). Subject should be fasting if possible.
- Perform a standard 12-lead ECG (Section 9.6.1).
- Collect a urine sample for pregnancy testing for women of childbearing potential (Section 7.8).
- Administer the C-SSRS (Section 9.6.3).
- Perform the TNmAS-MAL assessment (Section 8.2).
- Administer the EDSS assessment (Section 8.3).
- Administer the PGIC questionnaire (Section 8.1).
- Administer the USP questionnaire (Section 9.6.2).
- Collect unused study medication, assess compliance, and study drug accountability (Section 7.9).
- Record any AEs that have occurred (Section 9.7).
- Record all concomitant medications/therapies the subject is currently taking (Section 7.7).

7 STUDY TREATMENTS

7.1 Treatments Administered

All subjects will begin treatment with AERT at 40 mg per day (2 x 20 mg) for 3 days, then increase to 60 mg per day (3 x 20 mg) for 3 days, and then increase to 80 mg per day (4 x 20 mg). Once the subject has reached the maintenance dose, they will remain on that dose for approximately 1 year (Figure 2). The maintenance dose will be the highest tolerated dose, not exceeding 80 mg per day. The description of study drug kits and treatments is shown below in Table 2. Subjects may choose to taper study drug after Visit 3 if they experience adverse events. Direct consultation with the investigator site must be conducted before consideration for dose taper. Dose tapers should occur over the course of 9 days in 20 mg increments. Subjects should be encouraged to titrate back to 80 mg once adverse events subside or remain on the maximally tolerated AERT dose. Up to 3 dose tapers over the course of the clinical study are permitted.

Table 2: Study Drug Kits and Treatments, Study OS440-3005

Dosage form description:	Blue, round biconvex tablets.
Package description:	HDPE white bottles with 60 active 20-mg tablets.
Daily dose:	40, 60, and 80 mg arbaclofen depending on the study day. There will be a 9-day titration period (3 days at 40 mg/day, 3 days at 60 mg/day, and then increase to 80 mg/day), then an approximately 1-year maintenance period at 80 mg/day or the highest tolerated dose, followed by a 2-week taper period. Study tablets will be taken twice daily (BID).
Cumulative maximal dosage:	up to 28,420 mg arbaclofen
Manufacturer:	Osmotica Pharmaceutical US LLC, Marietta, GA 30062

7.1.1 Treatment Administration

The study medications will be administered orally twice daily (every 12 hours, or BID) without regard to food. Note: For the 60 mg/day titration, this means 1 x 20 mg AERT in the morning and 2 x 20 mg AERT in the evening.

Once the subject has reached the maintenance dose, they will remain on that dose for approximately 1 year. The maintenance dose will be the highest tolerated dose, not exceeding 80 mg per day. All attempts should be made for subjects to titrate to the 80 mg per day dose. If subjects experience untoward tolerability issues due to AERT, they may taper study drug only under the guidance of the study site (i.e., in 20 mg increments per week). Subjects may subsequently attempt study drug taper if the investigator deems this clinically appropriate. There will be no taper phase for subjects who solely achieve a 40 mg per day maintenance dose. Subjects may attempt to titrate to the target dose of 80 mg per day, if tolerability issues have resolved.

If a subject misses 7 or more consecutive days of dosing AND has taken less than 80% of their doses of study medication in a 42-day (6-week) period, then the subject must be discontinued (see Section 12.4).

7.1.2 Labeling of Study Drug

Study medication will be provided in labeled bottles. The labels will include all information required by federal and local regulations.

7.1.3 Storage of Study Drug

Arbaclofen extended-release tablets must be stored at 20°C to 25°C (68°F to 77°F), excursions permitted to between 15°C and 30°C (59°F to 86°F) (see USP Controlled Room Temperature. At study sites, all study medication must be stored, secured, and locked in a safe place.

7.2 Study Drug Accountability

The Principal Investigator will have overall responsibility for the use of the study drug. The Principal Investigator or designee will confirm receipt of the study drug by signature and date. A copy of this receipt must be returned to the Sponsor or designee when the contents of the drug shipment have been verified. In addition, an accurate study drug dispensing record that specifies the date and amount dispensed to each subject must be kept in accordance with the study drug accountability form. This inventory record must be available for inspection during an audit (e.g., by Sponsor or a regulatory agency). At the conclusion of the study, the Principal Investigator must provide a copy of this record to the Sponsor.

Under no circumstances will the investigator allow the investigational drugs to be used other than as directed by this protocol. The study medication must be protected from unauthorized access (e.g., in a locked storage facility). Qualified study personnel must use the specified randomization system to assign subjects to treatment. Reasons for digression from the expected dispensing regimen must also be recorded.

At the end of the study, all medication must be reconciled. Any unused medication will be inventoried by the investigator or designee and retained by the site until instructed otherwise by Sponsor.

7.3 Handling and Disposal of Study Drug

The study drug must be protected from unauthorized access (e.g., in a locked storage facility).

Any unused, partially used, or empty bottles of study drug will be returned to the Sponsor or designee by the time of the site's close-out visit. Receipt, distribution, and return of the study drug must be properly documented on forms provided by the Sponsor or designee.

7.4 Method of Assignment of Study Drug

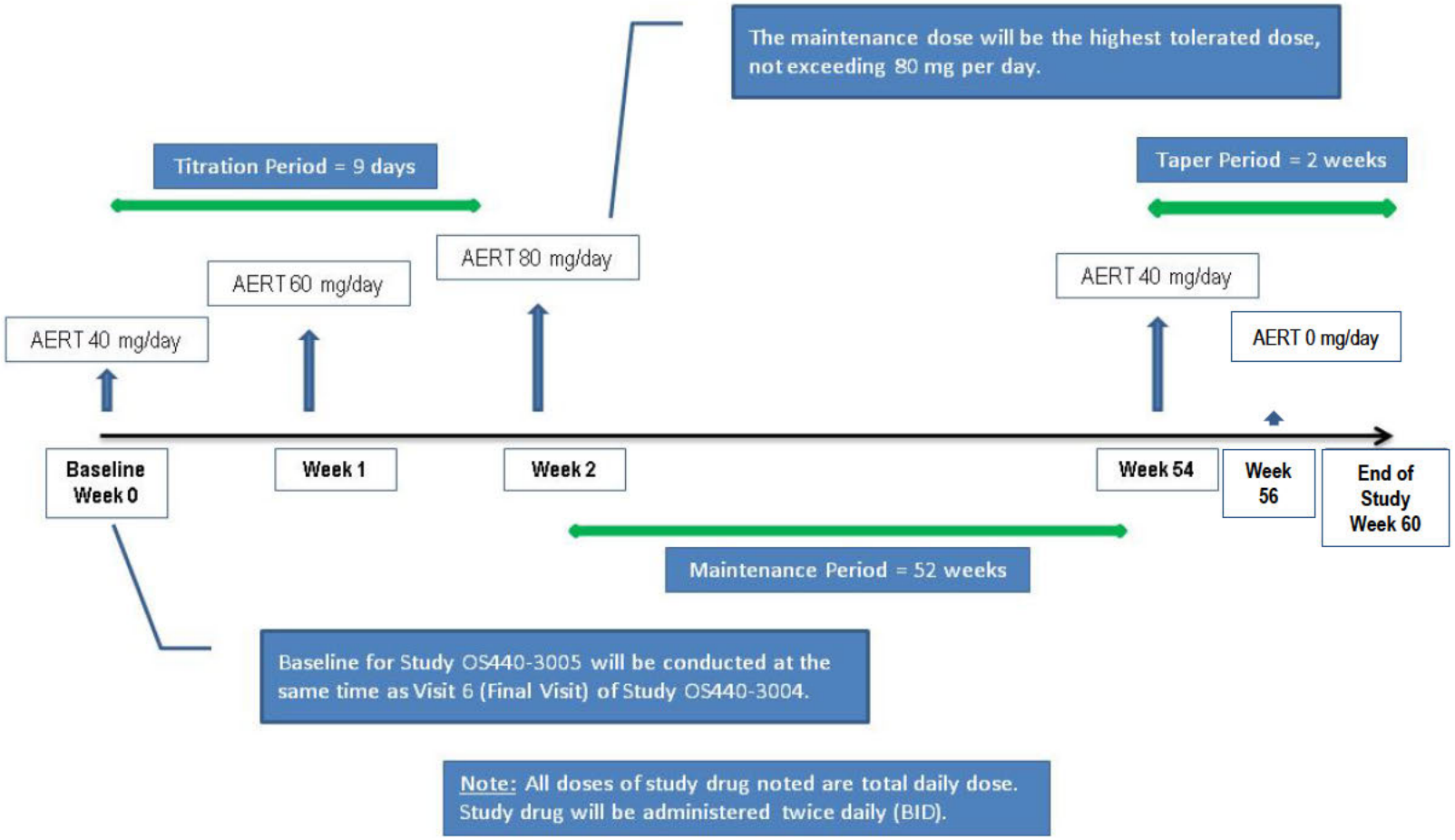
This is an open-label study and all subjects will begin treatment with AERT at 40 mg per day (20 mg BID) for 3 days, then increase to 60 mg per day (20 mg in the morning and 2 x 20 mg in the evening) for 3 days, and then increase to 80 mg per day (2 x 20 mg BID). Once the subject has reached the maintenance dose, they will remain on that dose for approximately 1 year. The maintenance dose will be the highest tolerated dose, not exceeding 80 mg per day. Subject will be allowed to taper the 80-mg/day dose for issues of tolerability on at most three occasions. If tolerability issues persist, the subject will be required to discontinue from the study.

After Baseline procedures have been completed, authorized site personnel will acknowledge that the applicable subject met all the specified inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2) and an enrollment number will be sequentially assigned.

7.5 Selection and Timing of Doses in the Study

There will be a 9-day titration period (3 days at 40 mg/day, 3 days at 60 mg/day, and 3 days at 80 mg/day), then a 1-year maintenance period, followed by a 2-week taper period. The maintenance dose will be the highest tolerated dose, not exceeding 80 mg per day. Subjects who discontinue early should also follow the 2-week taper period. Figure 2 presents the dosing regimen flowchart, including titration and taper, to be used during the study.

Figure 2: Flowchart of Open-Label Dosing Regimen, Study OS440-3005



At the end of treatment, a 2-week taper period will take place from Weeks 54 to 56. Subjects who discontinue early should also follow the 2-week taper period.

7.6 Emergency Unblinding

This is an open-label study.

7.7 Prior and Concomitant Therapy

The inclusion and exclusion criteria (Section 5.1 and 5.2, respectively) provide details on prohibited medications and food and the permitted duration since their last use prior to Baseline and/or study drug administration. For *de novo* subjects, all medications taken within 30 days before Baseline are to be recorded in the electronic case report form (eCRF). Eligible *de novo* subjects will undergo an up to 21-day washout period (no drug onboard) for withdrawal of all medications used for anti-spasticity and/or muscle relaxation prior to Baseline (see Inclusion Criterion 6). Any subject will be ineligible for the current open-label study if they are concomitantly using any of the medications listed in Appendix 5 (see Exclusion Criterion 5).

Table 3 presents the half-life, taper period, and washout period for specific anti-spasticity and/or muscle relaxation medications. Tapering of an existing anti-spasticity drug depends on the dose of the drug and other conditions. The investigator should use medical judgment to safely taper the dose. Under most conditions, the taper should take no more than 2 weeks. For anti-spasticity medications not shown in Table 3, please contact the medical monitor for discussions of the washout period.

Table 3: Taper and Washout Periods for Specific Anti-spasticity and/or Muscle Relaxation Medications, Study OS440-3005

Drug	Half-Life (hours)	Taper Period	Washout Period
Baclofen	3 to 5	3 to 14 days	1 day
Clonidine	12 to 16	3 to 14 days	3 days
Dantrolene	8 to 9	3 to 14 days	2 days
Gabapentin	5 to 7	3 to 14 days	2 days
Zanaflex	3	3 to 14 days	1 day
Diazepam	100	3 to 14 days	3 weeks

Other than anti-spasticity medications, all conventional medications regularly used for the treatment of MS and all non-pharmacological therapies (intended to alleviate spasticity, e.g., physiotherapy) are allowed provided they have been taken/administered for at least 1 month prior to enrollment and no dose adjustments are expected for the duration of this study.

Changes in either the dose or frequency of concomitant medications taken for the treatment of MS should not be made for the duration of this study. In the event a dose adjustment is needed for a concomitant medication, the investigator will contact the Sponsor to determine if the subject may remain in the study or needs to be withdrawn.

If a subject is receiving disease-modifying medications (especially interferons, see Inclusion Criterion 5), study visits should be scheduled prior to administration and, if possible, at a consistent time point during the study from when these drugs are administered in order to avoid interference with the temporary increase in spasticity that these medications may produce.

Subjects who experience an acute MS exacerbation/relapse (symptoms including but not limited to visual disturbance, dizziness, tingling, or extreme fatigue lasting greater than 24 hours and occurring at least 30 days after a previous relapse) requiring immediate therapy or adjustment in disease-modifying medication dose (e.g., oral or intravenous high-dose steroid therapy) will be discontinued from this study.

Other medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. The administration of all medication (including investigational products) will be recorded in the appropriate sections of the eCRF.

Data collection for concomitant medications will include information on indication, dose, route, dosing frequency, start date, stop date, and will continue throughout the study.

The investigator or study staff will ask the subject at every study visit whether they have taken any new medications or had changes in their current medications since the last study visit. It is the responsibility of the investigator to ensure that any change in concomitant medications during the study is recorded in the source documentation and entered in the eCRF.

7.8 Use of Contraception and Pregnancy Testing

Prior to study enrollment, females of childbearing potential and female partners of male subjects must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation/occlusion, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months). *De novo* premenopausal women of childbearing potential must have a negative serum pregnancy test within 21 days before Baseline and all enrolled subjects, if they are sexually active or become sexually active during the study, must use an effective method of birth control such as those listed below during the course of the study. Urine pregnancy testing will be done at Visits 1 through 8.

The following is not an all-inclusive list; the subject must discuss with the investigator the most appropriate form of birth control:

- Hormonal methods
    - Oral contraceptives
    - Implant
    - Injection
    - Transdermal patch

- Intravaginal ring

- Intrauterine device (hormonal or non-hormonal)
- Barrier methods
  - Condom (male or female) with spermicide
  - Diaphragm with spermicide
- Complete abstinence

7.9 Treatment Compliance

Subject compliance will be based on drug accountability information. Non-compliance will be defined as subjects taking less than 80% or more than 120% of prescribed study medication overall as assessed by the amount of study drug returned by the subject at the end of the study. If a subject misses 7 or more consecutive days of dosing AND has taken less than 80% of their doses of study medication in a 42-day (6-week) period, then the subject must be discontinued.

8 EFFICACY ASSESSMENTS

8.1 Patient Global Impression of Change

The PGIC is a standard instrument that is a well validated outcome measure. The 7-point PGIC measures change in the subject's overall status using the following categorical scale:

- 1 = Very much improved
- 2 = Much improved
- 3 = Improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse

The PGIC will be completed at the visits specified in Table 1. The PGIC is provided in Appendix 3.

8.2 Total Numeric-Transformed Modified Ashworth Scale

The TNmAS is considered the primary clinical measure of muscle spasticity in subjects with neurological conditions. It is a useful 6-point rating scale to measure abnormality in tone or the resistance to passive movements, since there is no clinically direct method for measuring spasticity.

When initially developed in the early 1960s (Ashworth 1964) to estimate the efficacy of anti-spastic drugs in subjects with MS, it was a 5-point scale, with a grade score of 0 to 4. In 1987, the grade "1+" was added and slight changes were proposed on the definitions of each score in order to increase the sensitivity of the measure and facilitate scoring. The new measure was then called the Modified Ashworth Scale (mAS) and it is considered the gold standard for measuring spasticity (Bohannon and Smith 1987).

Although there are no standardized guidelines for its use, it can be applied to muscles of both the upper or lower body. The rater should extend the client's limb from a position of maximal flexion to maximal extension until the first soft resistance is felt. Moving a subject's limb through its full range of motion should be done within 1 second by counting "one thousand and one."

It is suggested that the testing of the upper limbs should take place while the subject is lying supine, with the upper limbs parallel to the trunk, elbows extended, wrists in a neutral position, and the lower limbs positioned parallel to one another. Exceptions are made for the shoulder extensors, where the arm should be moved from extension to 90 degrees of flexion, and for the shoulder internal rotators, where the arm should be moved from neutral to a maximum external rotation. For the lower limbs, it is recommended that the subject be lying on their side. Specifically for testing the soleus muscle, the hips and knees should be positioned in 45 degrees of flexion and the ankle is moved from maximum plantar flexion to maximum dorsiflexion. For the gastrocnemius muscle, hips should be in 45 degrees of flexion with the knees in maximum extension and the ankle is moved from maximum plantar flexion to maximum dorsiflexion. For the quadriceps femoris muscle, knees and hips should be in maximal extension and the knee is moved from maximum extension to maximum flexion. Throughout testing, the subject should be instructed to remain calm and relaxed, and when repeated testing is undertaken, testing should be initiated at the same time of the day to minimize possible changes in spasticity levels due to medication interaction.

To arrive at the TNmAS-MAL score, the total numerical score of the most affected limb accounts for the sum of the 3 main joint muscular group scores.

The TNmAS-MAL assessment will be performed by the investigator who has been appropriately trained to perform and assess the TNmAS-MAL, and when possible, all TNmAS-MAL assessments should be performed for a particular subject by the same person throughout the study and always prior to any scheduled lab draw. The most affected limb will be determined by the investigator.

The TNmAS-MAL assessment will be done at the visits specified in Table 1. The mAS and TNmAS-MAL are provided in Appendix 1.

8.3 Expanded Disability Status Scale

The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time. It is widely used in clinical trials and in the assessment of people with MS. The scale was developed by John Kurtzke in 1983 as an advance from his previous 10-step Disability Status Scale (DSS) (Kurtzke 1983). The EDSS scale ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability.

EDSS steps 1.0 to 4.5 refer to people with MS who are able to walk without any aid and is based on measures of impairment in eight functional systems (FS): pyramidal (weakness or difficulty moving limbs), cerebellar (ataxia, loss of coordination, or tremor), brainstem (problems with speech, swallowing, and nystagmus), sensory (numbness or loss of sensations), bowel and bladder function, visual function, cerebral (or mental) functions, and other. Each FS is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability). EDSS steps 5.0 to 9.5 are defined by the impairment to walking.

The EDSS assessment will be done at the visits specified in Table 1. The EDSS is provided in Appendix 2.

9 SAFETY ASSESSMENTS

Safety will be assessed by the monitoring of AEs volunteered, observed, and elicited by general questioning in a non-suggestive manner. Changes in vital signs, clinical laboratory test results, 12-lead ECGs, the USP questionnaire, and the C-SSRS will also be assessed.

9.1 Medical/Surgical History

A complete medical and surgical history will be obtained at Baseline (Screening for *de novo* subjects), which will record previous respiratory, cardiovascular, gastrointestinal, hepatic, nephron-urologic, metabolic, allergic, infectious, gynecologic, musculoskeletal, endocrine, neurologic, psychiatric, dermatologic, allergic, hematologic, and any other diseases.

9.2 Vital Signs

Vital signs will be measured at all visits. Blood pressure measurements will be made using a sphygmomanometer with an appropriate cuff size for the individual subject.

To evaluate the potential of arbaclofen to trigger orthostatic hypotension, BP and heart rate will be measured twice at each study visit. Orthostatic testing should take place in a quiet room, preferably at a temperature between 20°C and 24°C (68°F to 75°F). Emptying the bladder before testing is also recommended. The diagnosis of orthostatic hypotension is established by measuring the BP in the supine and then in the standing position, at least 3 minutes apart, and noting a substantial drop accompanied by symptoms of dizziness or syncope. A positive response is considered if systolic BP falls below 20 mmHg and diastolic BP 10 mmHg of baseline. If symptoms occur, the subject should be returned to the supine position immediately.

Vital signs, including BP, heart rate, respiratory rate, and body temperature, will be measured after the subject has been in a supine position quietly for 10 minutes. Then, with the subject in a standing position, BP and heart rate will be measured again after the supine assessment is completed.

9.3 Physical Examination

A physical examination will be performed at Baseline (Screening for *de novo* subjects) and will include the following categories: general, head, ears, eyes, nose and throat, neck,

heart/cardiovascular, lungs/respiratory, abdomen, breast (performed by palpation), musculoskeletal (back and extremities), neurological, lymph nodes, and skin.

9.4 Weight and Height

Weight will be measured at Baseline (Screening for *de novo* subjects), at Visit 4 (Week 28), and at Visit 8 (Final Visit or Early Termination). Height will be measured only at Baseline. At each site the same balance will be used for all measurements. Subjects will wear only indoor clothing without shoes.

9.5 Clinical Laboratory Tests

A central laboratory will be used for this study. Blood draws for chemistry and hematology tests and urine samples for urinalyses will be collected and sent to the central laboratory. Table 4 presents the specific clinical laboratory tests to be evaluated.

All laboratory values that are outside of the normal range for that parameter will be so flagged when reported to the site. The investigator will annotate laboratory reports to indicate whether any abnormal laboratory value is considered clinically significant. Any abnormal laboratory value that is considered clinically relevant should be confirmed by a repeated laboratory test when possible. If a clinically significant laboratory abnormality requires treatment or is the reason for a subject being discontinued from the study, the abnormal result must be classified as an AE. If clinically relevant and considered an AE, the event must be followed until resolution or as long as medically necessary and be recorded on the AE page of the eCRF.

Table 4: Clinical Laboratory Tests, Study OS440-3005

Hematology	Urinalysis	Serum Chemistry
Hematocrit	Bilirubin	Alanine aminotransferase (ALT)
Hemoglobin	Blood	Albumin
Platelet count	Glucose	Alkaline phosphatase
Red blood cell (RBC) count	Ketones	Aspartic acid transaminase (AST)
White blood cell (WBC) count with differential	Leukocytes esterase	Bicarbonate
	Specific gravity	Blood urea nitrogen (BUN)
	Color	Chloride
	pH	Creatinine
	Protein	Creatinine kinase
	Microscopic examination of urine: • Epithelial cells • Casts (RBC, WBC, etc.) • Red blood cells • White blood cells	Glucose Potassium Sodium Total bilirubin (if elevated, obtain direct bilirubin) Uric acid
	Urine pregnancy test (at the site)	

ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = white blood cell

Samples for clinical hematology, serum chemistry, and urinalysis will be obtained for each subject and sent to a central laboratory at the visits specified in Table 1. Site personnel will do a routine urinalysis by dipstick on site and the central laboratory will do a complete microscopic urine examination. Site personnel will also complete a urine pregnancy test for female subjects of childbearing potential on site at the visits specified in Table 1 (see Section 7.8 regarding serum pregnancy testing in premenopausal women of childbearing potential at Baseline [Screening for *de novo* subjects]).

Sample collection kits, requisition slips, and shipping boxes will be supplied by the central laboratory. Sample collection procedures and shipping instructions will be detailed in the laboratory manual. Study centers must be equipped to store the samples according to the laboratory manual procedures before shipping samples to the central laboratory.

9.6 Other Safety Assessments

9.6.1 Electrocardiograms

A standard 12-lead ECG will be performed on subjects in the supine position. Subjects will have rested in the supine position for at least 5 minutes prior to the ECG. The time at which the subject assumed the supine position will be recorded to confirm the rest time. ECGs will be done at the visits specified in Table 1.

9.6.2 Urinary Symptom Profile© Questionnaire

The USP is a health-related quality of life questionnaire developed in 2005 by the French Association of Urology and validated in 2008 (Haab et al 2008). It is composed of 13 items in 3 dimensions to assess urinary symptoms among adults (both men and women) with stress, urge, overactive bladder, or urinary obstructive symptoms. It is administered with a time frame over the past 4 weeks. The USP is a valuable tool for self-administration by the subject to complement clinical measures and diagnosis due to it being a valid and reliable questionnaire providing comprehensive evaluation of all urinary disorders and their severity. It also allows the pathology screening and contributes to the differential diagnosis of these symptoms. Due to the potential risk of arbaclofen to produce urinary problems, mainly at the bladder level (as seen in some animal toxicological studies; see the current arbaclofen Investigator's Brochure [IB]), the utilization of this questionnaire has been implemented in the context of this study to monitor urinary symptomatology and rule out any complication that could be developed during the course of the study. An increase of 4 points in the total USP score from the previous visit will be considered an AE.

The USP questionnaire will be completed by the subject at the visits specified in Table 1. The USP is provided in Appendix 6.

9.6.3 Columbia–Suicide Severity Rating Scale

The C-SSRS will be administered by the investigator or a qualified designee trained in its administration. The C-SSRS is a standardized instrument that was developed to assess the severity of and monitor changes in suicidal ideation and behavior. Four constructs are measured. The first is severity of ideation rated on a 5-point ordinal scale. The second is intensity of ideation, which

comprises 5 items (frequency, duration, controllability, deterrents, and reason for ideation) each rated on a 5-point ordinal scale. The third is behavior rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. The fourth is lethality, which assesses actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale.

The C-SSRS assessment will be done at the visits specified in Table 1. The C-SSRS is provided in Appendix 4.

9.7 Adverse Events

9.7.1 Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or observed by the investigator. AEs will be recorded at each visit throughout the study. All AEs will be recorded on the AE log of the eCRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Subjects should be asked whether, since the time of the last observation or visit, they had any of the following:

- Experienced any changes in well-being.
- Used any new medications.
- Changed medication regimens (both prescription and over-the-counter).
- Were admitted to a hospital or had any accidents.

All questions should be of a general nature and should not suggest symptoms.

When an AE is suspected, all relevant evaluations will be performed and appropriate treatment provided. Additional follow-up will be done as necessary (Section 9.7.4) and recorded in the subject's source documents, and the results will be provided to the Sponsor.

9.7.2 Adverse Event Definitions

9.7.2.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease that appears or worsens in a subject after the subject signs the ICF for a clinical study.

Examples of what may be considered an AE include any of the following:

- A new illness.

- An exacerbation of a sign or symptom of an underlying condition or of a concomitant illness unrelated to participation in the clinical study or an effect of the study drug or comparator drug.

No causal relationship with the study drug is implied by the use of the term "adverse event." An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. (If the event meets the criteria for a SAE, such as an extended hospitalization, it will be considered an SAE). Conditions leading to unplanned surgical procedures may also be AEs.

9.7.2.2 Serious Adverse Events

An SAE is any AE that:

- Results in death.
- Is life-threatening.

  Note: The term "life-threatening" refers to any AE that, as it occurs, puts the subject at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe.

- Results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the subject's underlying medical condition prior to entry into the study).
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of a subject
- Is another serious event (important medical events)

  Note: Important medical events may not be immediately life-threatening or result in death or hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse.

9.7.2.3 Severity of Adverse Events

"Severity" of the AE refers to the extent to which an AE affects the subject's daily activities and differs from "Serious", which is a regulatory classification. Severity will be categorized according to the following criteria:

- **Mild:** The symptom has a negligible effect or no impairing effect on the subject's normal function.

- **Moderate:** The symptom impairs the subject's normal function to some extent.

- **Severe:** The symptom has an obvious, significantly impairing effect on the subject's normal function.

9.7.2.4 Relationship of Adverse Events to Study Treatments

"Causality" refers to the relationship of the AE to study drug and will be categorized according to the following criteria:

- **Unlikely:** There is no medical evidence to suggest that the AE may be related to study drug usage, or there is another more probable medical explanation.

- **Possible:** There is medical evidence to suggest that there is a reasonable possibility that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause.

- **Probable:** There is strong medical evidence to suggest that the AE is related to study drug usage.

9.7.2.5 Adverse Events Expectedness

Expected AEs are defined as those described in the arbaclofen IB. If an event increases in intensity or severity from that described in the IB, it will be considered unexpected.

9.7.3 Reporting Adverse Events

Adverse events that occur from the time of informed consent through completion of the last study visit should be reported. Any AE that the investigator becomes aware of that occurs within 30 days of study completion or withdrawal should also be reported.

Any SAEs occurring in a subject receiving study medication must be reported to the Sponsor within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. This reporting must be done by faxing the appropriate completed form (SAE form or Exposure during Pregnancy form) to the Sponsor. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:

Additional PSI-CRO international safety reporting lines are provided in Appendix 7.

9.7.4 Adverse Event Follow-Up

Adverse events that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the investigator), or for 30 days, whichever is shorter. Investigators and the Sponsor will decide if longer follow-up is appropriate on a case-by-case basis. Subjects who experience any clinically significant AE will remain under medical supervision until the investigator or the Sponsor's Medical Monitor deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

Laboratory values that are abnormal and not assessed as AEs may be followed at the discretion of the investigator or the Sponsor's Medical Monitor until resolved or stabilized.

9.7.5 Pregnancy Reporting

Prior to study enrollment, females of childbearing potential and female partners of male subjects must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The ICF that the subject signs must document this discussion.

If a subject or investigator suspects that the subject may be pregnant prior to study drug administration, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study.

A urine pregnancy test will be performed on all females of childbearing potential as described in Section 7.8.

During the study, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that the subject may be pregnant at any time before or during the study, the study drug must be withheld until the results of laboratory pregnancy testing are available. The Sponsor and site monitor must be notified and relevant information

collected on the appropriate form. If pregnancy is confirmed, the subject must be withdrawn from the study and the Sponsor and site monitor notified. Additional relevant information about the confirmed pregnancy will be recorded on the appropriate form(s); pregnancy will not be captured as an AE.

The subject should be followed until the outcome of the pregnancy is known.

9.8 Appropriateness of Safety Measurement

The safety assessments to be utilized in this study are standard safety measures in clinical trials.

10 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will oversee study subject safety with respect to AEs and clinically important lab values. The committee will include three individuals with collective experience and knowledge about clinical trial conduct, study subject safety, MS, and bladder dysfunction, a condition common in MS subjects. DSMB members will be independent of the Sponsor, study sites, and the managing vendors, and will have no other role in the trial. The DSMB will convene after 33%, 66%, and 100% of the trial is enrolled. The role of the DSMB will be governed by a DSMB charter.

11 STATISTICAL DESIGN AND ANALYSIS

11.1 Statistical Analysis Plans

A detailed Statistical Analysis Plan (SAP) will be finalized prior to study termination.

Descriptive statistics (n, mean, median, standard deviation [SD], minimum, and maximum for continuous data; frequencies and percentages for categorical data) will be used to summarize study data. Unless specified otherwise, all statistical testing will be two-sided and performed using a significance level of 0.05.

11.2 Analysis Populations

The following population will be defined for analysis:

- Safety population: Includes all subjects who receive at least one dose of open-label study treatment and have at least one post-dose visit. Subjects will be analyzed according to the treatment received. This population will be used for all safety and efficacy analyses.

11.3 Determination of Sample Size

In total, approximately 300 subjects are to be enrolled in this study (i.e., both rollover and *de novo* subjects). It is anticipated that approximately 50% of subjects randomized into the double-blind study (Study OS440-3004) may roll over into this open-label study, and US subjects who did not participate in the previous double-blind Study OS440-3004 (i.e., *de novo* subjects) may also enroll into the current study. The number of subjects at each site will be determined primarily by the rate of recruitment in Study OS440-3004. No statistical rationale for subject number is provided.

The sponsor has previously completed a 1-year, open-label safety study (Study OS440-3003) at the 40-mg per day dose. In Study OS440-3003 a total of 148 subjects were treated. Study OS440-3005 is designed to enrich the existing safety database and provide long-term safety and tolerability data at the maximum daily dose of 80 mg/day. Target recruitment includes at least 100 subjects treated at 6 months and 50 subjects treated for 1 year at 80-mg per day.

11.4 Efficacy Analyses

11.4.1 Efficacy Endpoints

11.4.1.1 Patient Global Impression of Change

Descriptive summaries for PGIC scores will be tabulated by study visit and for change from baseline.

11.4.1.2 Total Numeric-Transformed Modified Ashworth Scale

Descriptive summaries for TNmAS-MAL scores will be tabulated by study visit and for change from baseline.

11.4.1.3 Expanded Disability Status Scale

Descriptive summaries for EDSS scores will be tabulated by study visit and for change from baseline.

11.5 Safety Endpoints

Safety endpoints will be reported on the Safety population. Subjects will be reported according to the treatment they actually received. Safety assessment will be based on descriptive statistics and individual subject listings. No statistical tests will be performed for any of the safety assessments.

All reported AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) system organ classifications (SOCs) and preferred terms (PTs). If a subject reports multiple events of a single PT, the greatest severity and strongest investigator assessment of relationship to study treatment will be assigned to that PT. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study drug. Summaries of treatment-emergent AEs (TEAEs) will include any AEs reported beginning with the first dose of study treatment on Day 1. The occurrence of TEAEs will be summarized by treatment group using SOCs, PTs, and severity. Separate summaries of treatment-emergent SAEs, TEAEs considered related to study treatment, and events leading to the discontinuation of study drug will be generated.

Descriptive summaries of vital signs, clinical laboratory results, USP results, and the C-SSRS results will be presented by study visit and treatment group. The number and percentage of subjects with treatment-emergent clinical laboratory abnormalities will be summarized by treatment group. Normal range clinical laboratory shifts from baseline to end of study will be summarized by treatment group.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary. These data will be summarized by treatment group. Previous and concomitant medications will be presented in a data listing.

Subject disposition will be presented for all subjects. The numbers of subjects who complete the study and who discontinue early from the study will be provided. The reasons for early discontinuation will also be presented.

11.6 Interim Analysis

No interim analysis is planned.

12 STUDY MANAGEMENT

12.1 Monitoring

The investigator will be responsible for preparing and maintaining adequate and accurate source documents (medical records, ECGs, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject treated with the study drug. The investigator will allow representatives of the Sponsor, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) to have direct access to all documents pertaining to the study. The investigator is to immediately notify the Sponsor of any regulatory authority inspections. The investigator will be informed about the outcome of any Sponsor audit.

This study will be monitored regularly, by or under supervision of a monitor from the Sponsor. The frequency of monitoring visits will be agreed upon by the Sponsor's representative and the study site.

Monitoring visits will take place on a regular basis according to the enrollment rate and number of subjects enrolled at each investigational site. During these visits, the monitor will check the completion of the eCRF entries, compliance with the study protocol and with Good Clinical Practice - International Conference on Harmonization (GCP-ICH), and their agreement with the source data. The monitor will also verify the correct use of the study drug. At a final visit, the monitor will check all remaining material including the remaining quantities of the study drug and will organize their return to the Sponsor or designee. At each visit, the investigator and staff will be expected to cooperate with the Sponsor's representative(s) for the purposes of review and verification of protocol compliance, AE reporting, eCRFs, source documents, clinical supplies and inventory records, and any additional records as may have been previously arranged between the investigator and the Sponsor's representative(s).

The investigator and/or other designated study personnel are expected to contact the Sponsor with any study concerns and/or questions. Contact information is provided in the Study Reference Manual for the site.

12.2 Protocol Amendments

The Sponsor may propose to amend this protocol at any time.

No change to the protocol will be implemented until the Sponsor and the IRB/IEC have reviewed and approved the amendment.

In the event of an emergency, the investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

12.3 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the IRB/IEC approved protocol (intentional or unintentional). Protocol deviations are to be reported to the IRB/IEC according to the IRB/IEC guidelines.

12.4 Withdrawal of Subjects

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subject withdrawal requires a 2-week dose taper. A subject will be considered to have discontinued prematurely if he/she withdraws prior to completing Visit 8 (Final Visit). If a subject misses 7 consecutive days AND has taken less than 80% of their doses of study medication in a 42-day (6-week) period, then the subject must be discontinued. Subjects may also be withdrawn from the study because of any of the following:

- **Adverse Event:** An AE that, in the opinion of the investigator or Sponsor, suggests that continued participation in the study is not in the subject's best interest for safety reasons (also see Section 10). All AEs that are present when the subject withdraws from the study will be followed as described in Section 9.7.4.

- **Medical Condition:** Any medical condition that, in the investigator's judgment, would increase the risk or interfere with the evaluation of study objectives.

- **Lost to Follow-up:** Confirmed at minimum by two phone calls and a traceable letter without answer.

- **Subject Request:** Subject requests for any reason to be withdrawn or withdraws his/her consent. Every effort should be made to determine the reason for the withdrawal request (e.g., AE, lack of efficacy, scheduling issues, etc.).

- **Protocol Deviation:** A subject may be withdrawn from the study at the discretion of the investigator or Sponsor due to poor compliance with protocol requirements that may compromise the study results or subject safety.

- **Enrollment in Another Study:** Enrollment in other protocols involving research drugs, medical devices, or surgeries.

- **Other Anti-spasticity Treatment:** Starting any other pharmacological anti-spasticity treatment during the study.

- **Relapse:** Subjects who experience an acute MS exacerbation/relapse (symptoms including but not limited to visual disturbance, dizziness, tingling, or extreme fatigue lasting greater than 24 hours and occurring at least 30 days after a previous relapse) requiring immediate therapy or adjustment in disease-modifying medication dose (e.g., oral or intravenous high-dose steroid therapy).

- **Other:** Other reasons include but are not limited to: Investigator decision that it is in the subject's best interest to be withdrawn, administrative reasons, relocation of subject, etc. If a subject or the partner of a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through conclusion of the pregnancy (see Section 9.7.5).

When possible, a decision to discontinue a subject from the study should first be discussed with the Sponsor's Medical Monitor. If a subject is prematurely discontinued after randomization and prior to the final scheduled visit, every effort should be made to perform all of the Visit 8 assessments (Table 1). The reason(s) for early withdrawal must be recorded in the eCRF. Subjects withdrawn from the study will not be replaced.

12.5 Termination of the Study

The study may be terminated at any time at the request of the Sponsor or a regulatory authority, with proper and timely notification of all parties concerned. The IRB/IEC will be informed promptly and the Sponsor or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements. Otherwise, the study is considered terminated upon completion of all subject treatments and evaluations.

12.6 Publication Policy

The data obtained in this study are the property of the Sponsor, who will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor may be of a strictly confidential nature, any manuscript or other presentation of data must first be reviewed by the Sponsor before its submission.

13 ETHICS

13.1 Conduct of the Study

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP, 1997; the US Title 21 CFR parts 50, 56, and 312; and the ethical principles that have their origin in the Declaration of Helsinki. The study will not begin until all of the requirements of the appropriate regulatory authorities have been fulfilled.

13.2 Institutional Review Boards and/or Independent Ethics Committees

This protocol (and any changes), all consent forms, and subject consent procedures must be reviewed and approved by a properly constituted IRB/IEC. The information presented to the IRB/IEC at the time initial approval is sought must include any plans for subject recruitment that

involve advertising or other direct contact with potential subjects outside of the doctor-subject relationship. A letter of approval issued by the IRB/IEC must be sent to the Sponsor prior to initiation of the study. Any changes made to the protocol must be approved by the IRB/IEC prior to implementation, except where needed to eliminate a potential imminent safety hazard to the subject. In this case, immediate implementation may take place followed by IRB/IEC approval. Review and approval by the IRB/IEC for continuation of the study must take place at least once a year.

13.3 Written Informed Consent

The investigator or designee will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential benefits and risks of participation to each subject prior to his/her entry into the study (i.e., before examinations and procedures associated with selection for the study are initiated). Each subject will have ample opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he/she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the ICF may enter the study. The ICF must be reviewed and approved by the Sponsor and the IRB/IEC prior to its use.

The original signed ICF will remain in the investigator's files. The investigator or designee will indicate in each subject's source documents that he/she has informed the subject about the study and its procedures, the subject has signed and dated the ICF, and the subject has been given a copy of the signed ICF. The investigator or designee will inform subjects of any new information that may be relevant to the subject's willingness to continue in the study.

13.4 Subject Confidentiality

The Sponsor ensures that the following have permission to review all study-related documents: monitor, auditor, IRB/IEC, and regulatory authorities. The subject's identity and study-related records will remain confidential throughout the duration of the study data collection and reporting process.

A unique subject identification code will be assigned to each potential study subject. The identification code protects the subject's identity and is used in lieu of the subject's name when reporting subject data. The data will always maintain the confidentiality of the subject.

The investigator or designee will review the subject data, which will be referenced using the subject identifier. At the conclusion of the study, the data obtained may be presented to regional regulatory authorities but the subject's identity will not be revealed. In addition, if any clinical data obtained from the study are published in scientific journals or presented at scientific meetings, the subject's identity will not be revealed.

13.5 Records Retention

The investigator must maintain essential study documents (protocol and amendments, source documentation corresponding to all information contained in the eCRFs, signed ICFs, relevant

correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same time period. Custody of the records may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor. The investigator must contact the Sponsor prior to disposing of any study records.

13.6 Financing

Funding for this study will be agreed between the investigator and the Sponsor and will be confirmed in writing before the study starts.

Completion of Financial Disclosure Forms will be required before the study starts. Any additions to the primary site personnel will necessitate the completion of new Financial Disclosure Forms. This information will also be collected at site closure and 1 year after the completion of the study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and investigator will take all steps possible to ensure the accuracy, consistency, completeness, and reliability of the data, including participating in an investigator meeting and/or site initiation visit, routine site monitoring, review of eCRFs against source documents, and quality control checks.

In addition, a representative from the Sponsor's Clinical Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and CROs, the clinical database, and the final study report.

15 DATA HANDLING AND RECORD KEEPING

This study will use web-based eCRFs developed through a validated, Electronic Records/Electronic Signatures-compliant platform (US Title 21 CFR Part 11). The Sponsor's Clinical Data Management department or designee will create the eCRFs and corresponding clinical database based on the final protocol.

All site personnel who will be using this system will receive formal training on the system, after which each person will be issued a unique username and password. Only the person who owns the username and password will enter the system using that username and password. For data security reasons and to be in compliance with regulatory guidelines, usernames and passwords are not transferable.

The investigator is responsible for all data entered via the remote data capture (RDC) system eCRFs and must confirm the accuracy of the data by electronically approving (signing) the eCRFs. This responsibility includes the timely completion and accuracy of the data entered into the eCRFs by their site personnel as well as the review and approval of some data entered directly into the

database (e.g., clinical laboratory results) by an external vendor. The Sponsor will review the database to identify data errors or inconsistencies, which will be posted in the RDC system as queries for resolution. In addition, the Sponsor may make obvious corrections to the data in the database (e.g., obvious errors in dates).

16 REFERENCE LIST

Ashworth B. Preliminary Trial of Carisoprodol in Multiple Sclerosis. Practitioner. 1964;192:540-542.

Haab F, Richard F, Amarenco G, Coloby P, Arnould B, et al. Comprehensive evaluation of bladder and urethral dysfunction symptoms: development and psychometric validation of the Urinary Symptom Profile (USP) questionnaire. Urology. 2008;71(4):646-656. DOI: 10.1016/j.urology.2007.11.100. Epub 2008 Mar 3.

Kurtzke J. Rating Neurologic Impairment in Multiple Sclerosis: an Expanded Disability Status Scale (EDSS). Neurology. 1983;33(11):1444-1452.

Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292–302. doi: 10.1002/ana.22366

Appendix 1. Modified Ashworth Scale

Score	Modified Ashworth Scale
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension /abduction or adduction, etc.
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM (range of movement).
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.
3	Considerable increase in muscle tone, passive movement difficult.
4	Affected part(s) rigid in flexion or extension (abduction or adduction, etc.)

Source: Bohannon and Smith 1987

Scoring: (Total Numeric-transformed mAS score)

Ashworth Score	0	1	1+	2	3	4
	↓	↓	↓	↓	↓	↓
Numerical Score	0	1	2	3	4	5

Numerical Score

Upper Extremities:	**R**	**L**	**Lower Extremities:**	**R**	**L**
Shoulder			Hip		
Elbow			Knee		
Wrist			Ankle		
Numerical Total:			**Numerical Total:**		

Appendix 2. Expanded Disability Status Score

0.0	Normal neurological exam (all grade 0 in all Functional System [FS] scores*).
1.0	No disability, minimal signs in one FS* (i.e., grade 1).
1.5	No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5	Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).
9.0	Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).
10.0	Death due to MS.

EDSS = expanded disability status scale; FS = Functional System

* Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the FS score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in FS scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Appendix 3. Patient Global Impression of Change Scale

PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Date _____ Patient Name _____ Date of Birth_____

Chief Complaint (Presenting Problem): _____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition? Please circle the number below, that matches your degree of change since beginning care at this clinic for the above stated chief complaint.

No change	Almost the same	A little better	Somewhat better	Moderately better	Better	A great deal better
1	2	3	4	5	6	7

Explanation:

1 = No change (or condition has got worse)
2 = Almost the same, hardly any change at all
3 = A little better, but no noticeable change
4 = Somewhat better, but the change has not made any real difference
5 = Moderately better, and a slight but noticeable change
6 = Better, and a definite improvement that has made a real and worthwhile difference
7 = A great deal better, and a considerable improvement that has made all the difference

Patient's signature: X _____

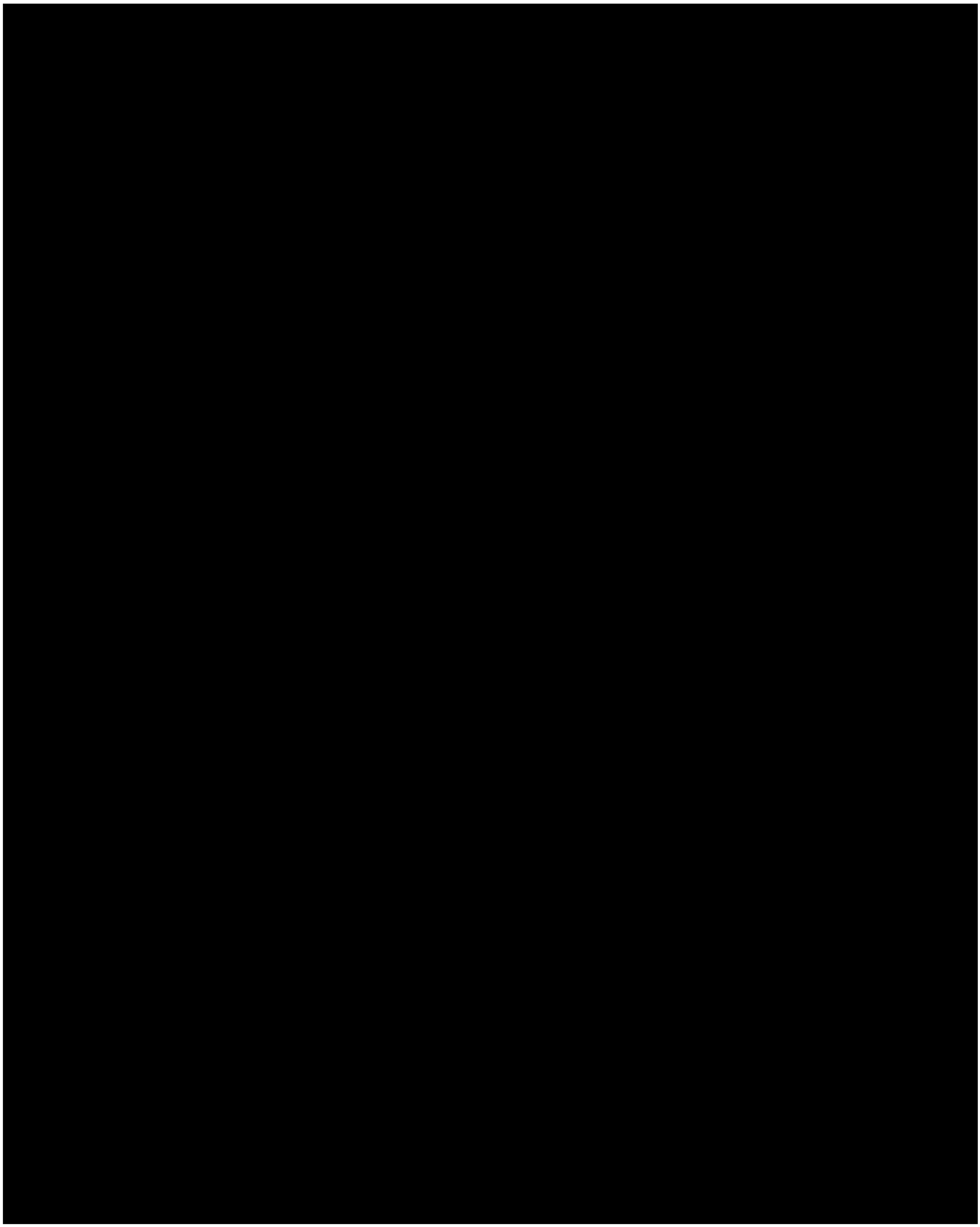
Do not write in this box - FOR OFFICE USE ONLY.

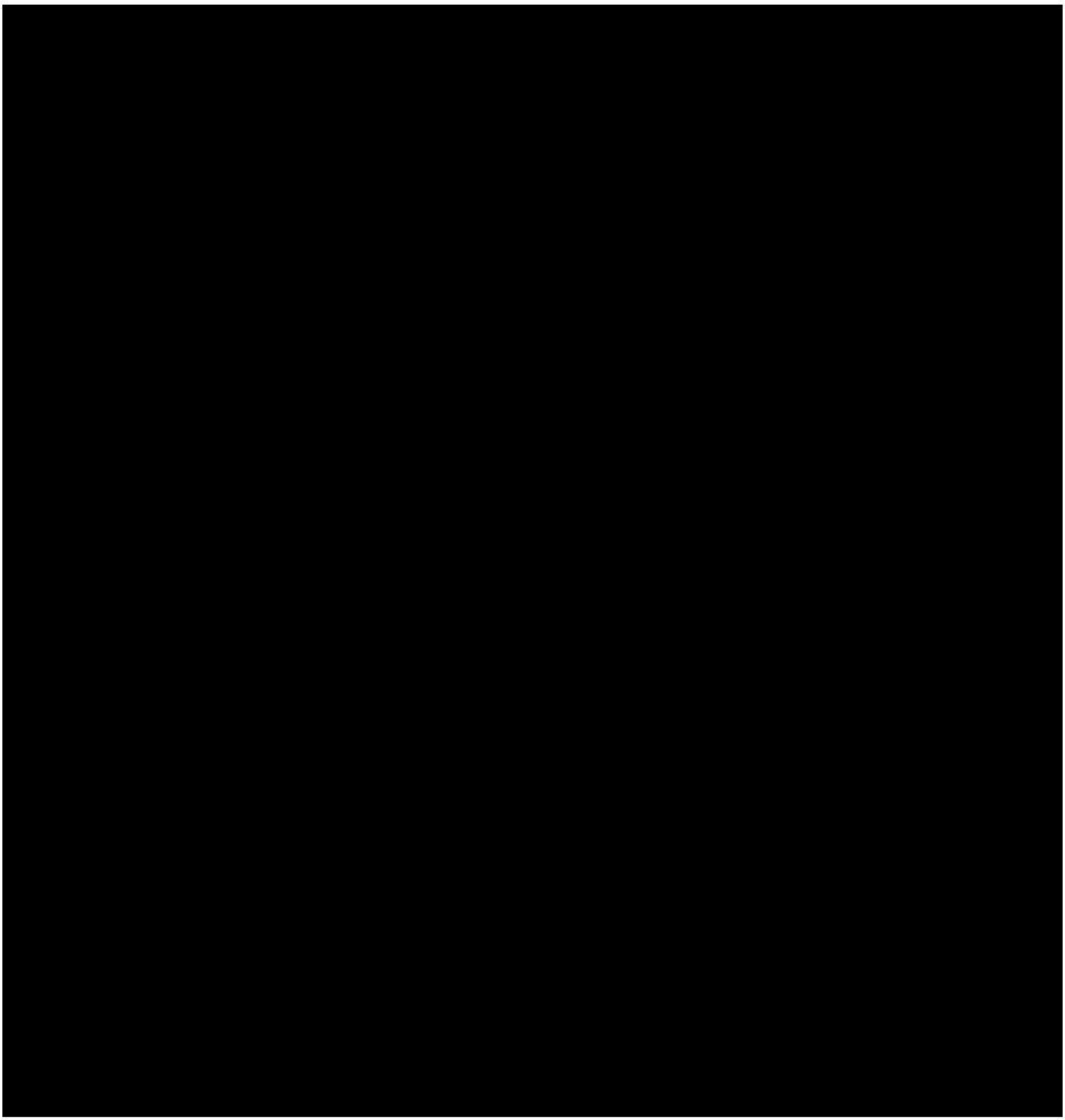
NOTE TO HEALTH CARE PROVIDER

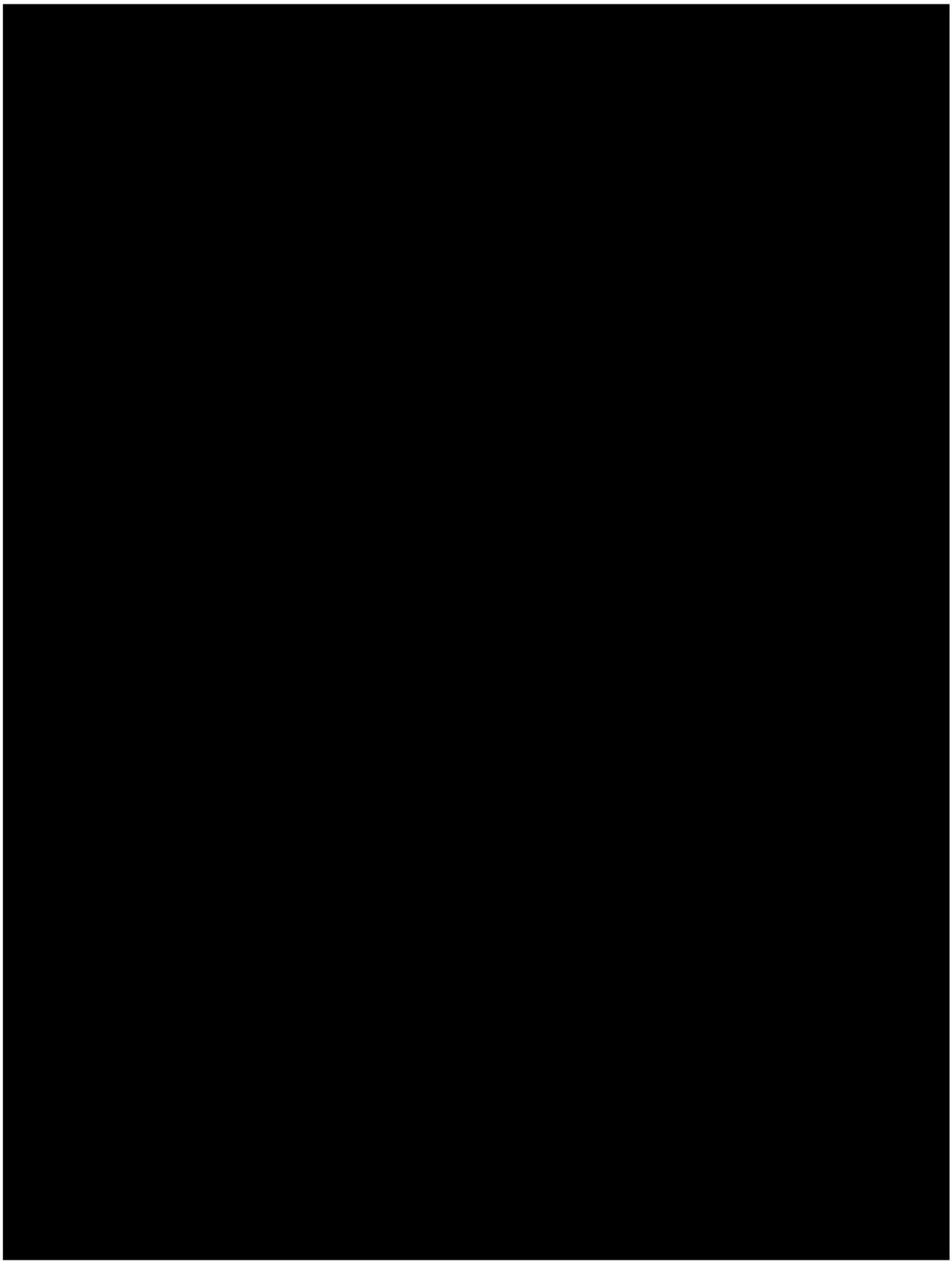
A significant, favorable change is a score of 5- 7
No significant change is a 1-4 response.
Note, this is a dichotomous scale (5-7 = yes; 1-4 = no).
A 2-point change is significant from their last reported score.

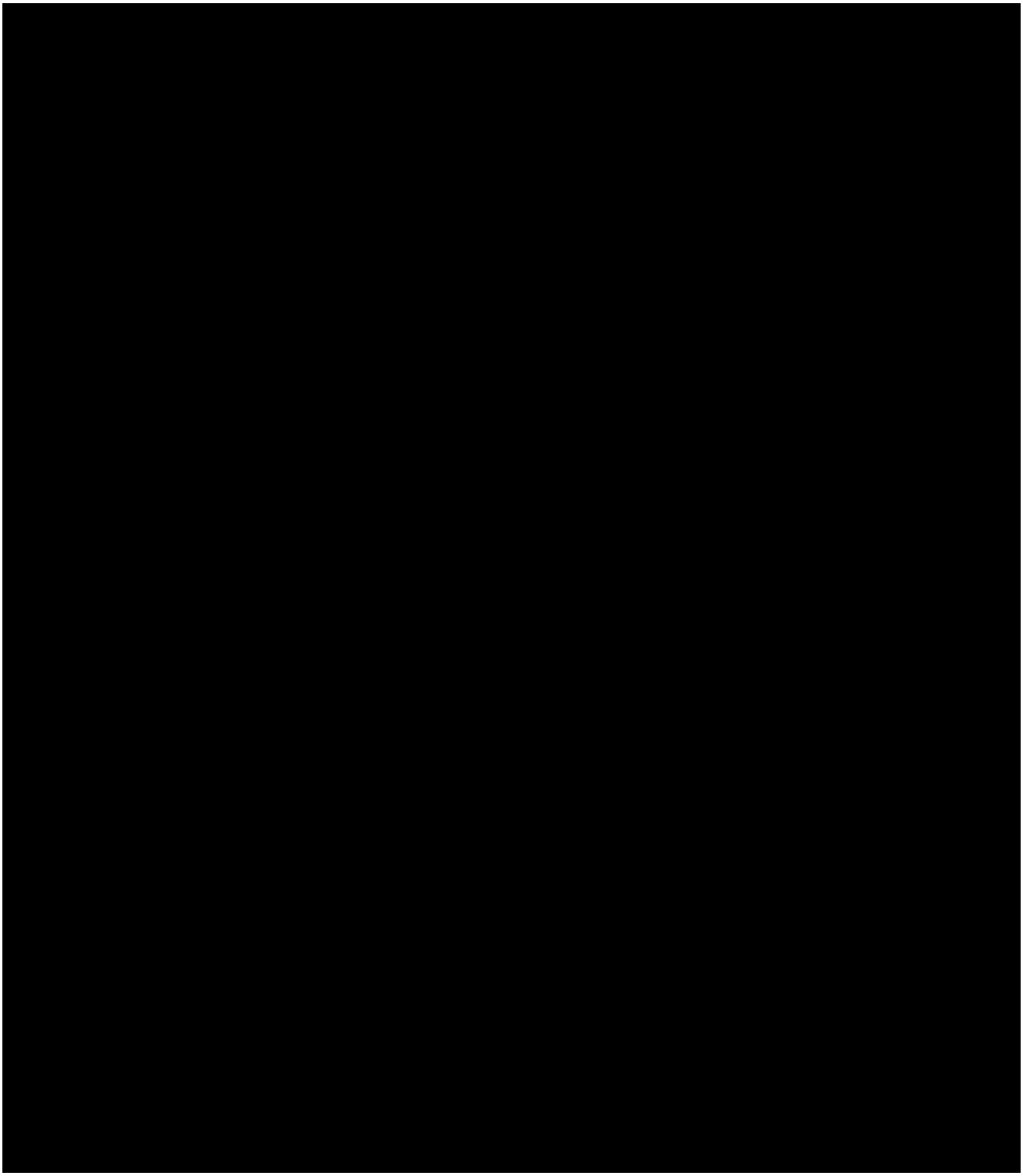
Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of Manipulative Physiological Therapeutics (IMPT) 2004;27:26-35.

Appendix 4. Columbia–Suicide Severity Rating Scale

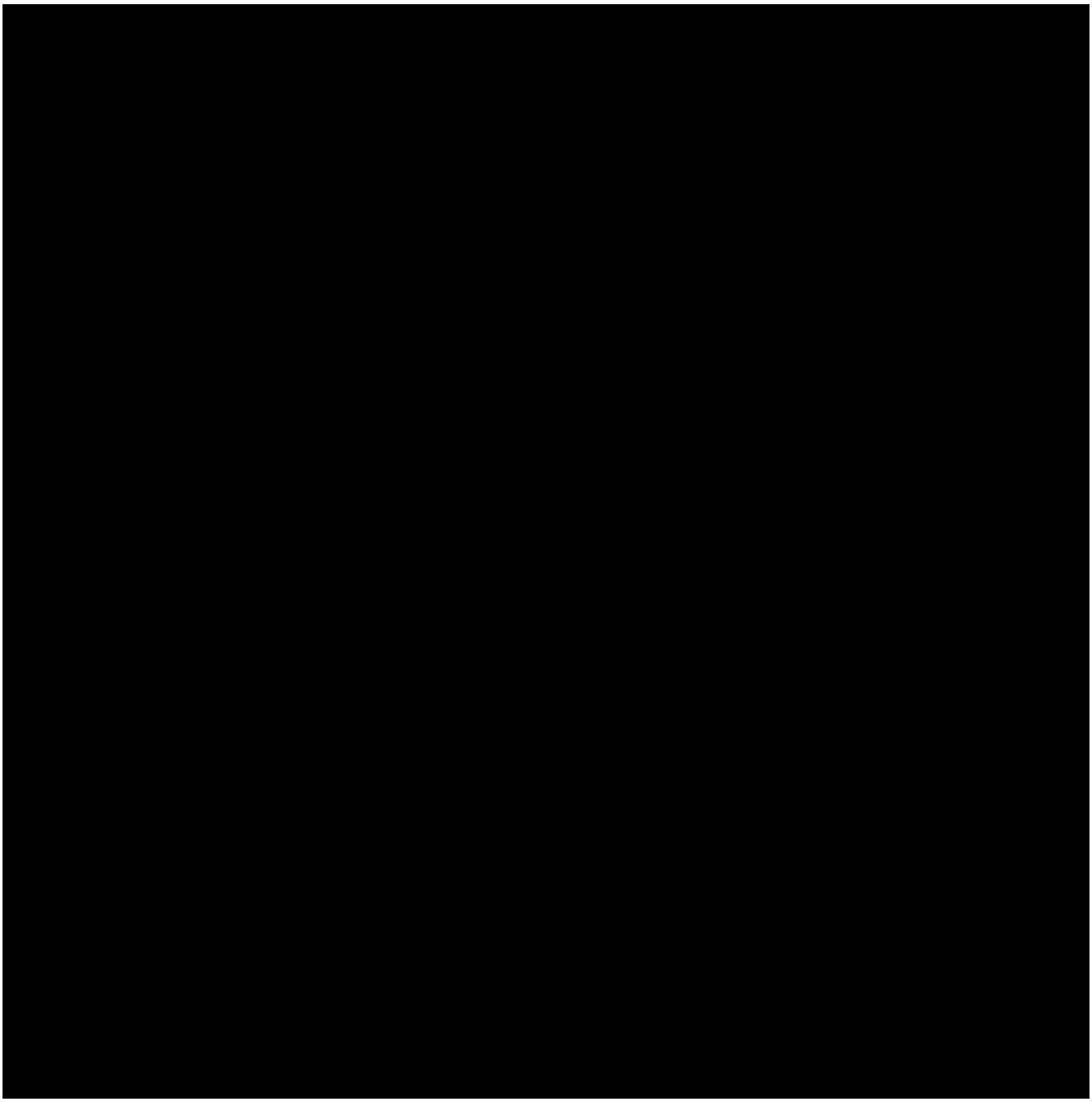


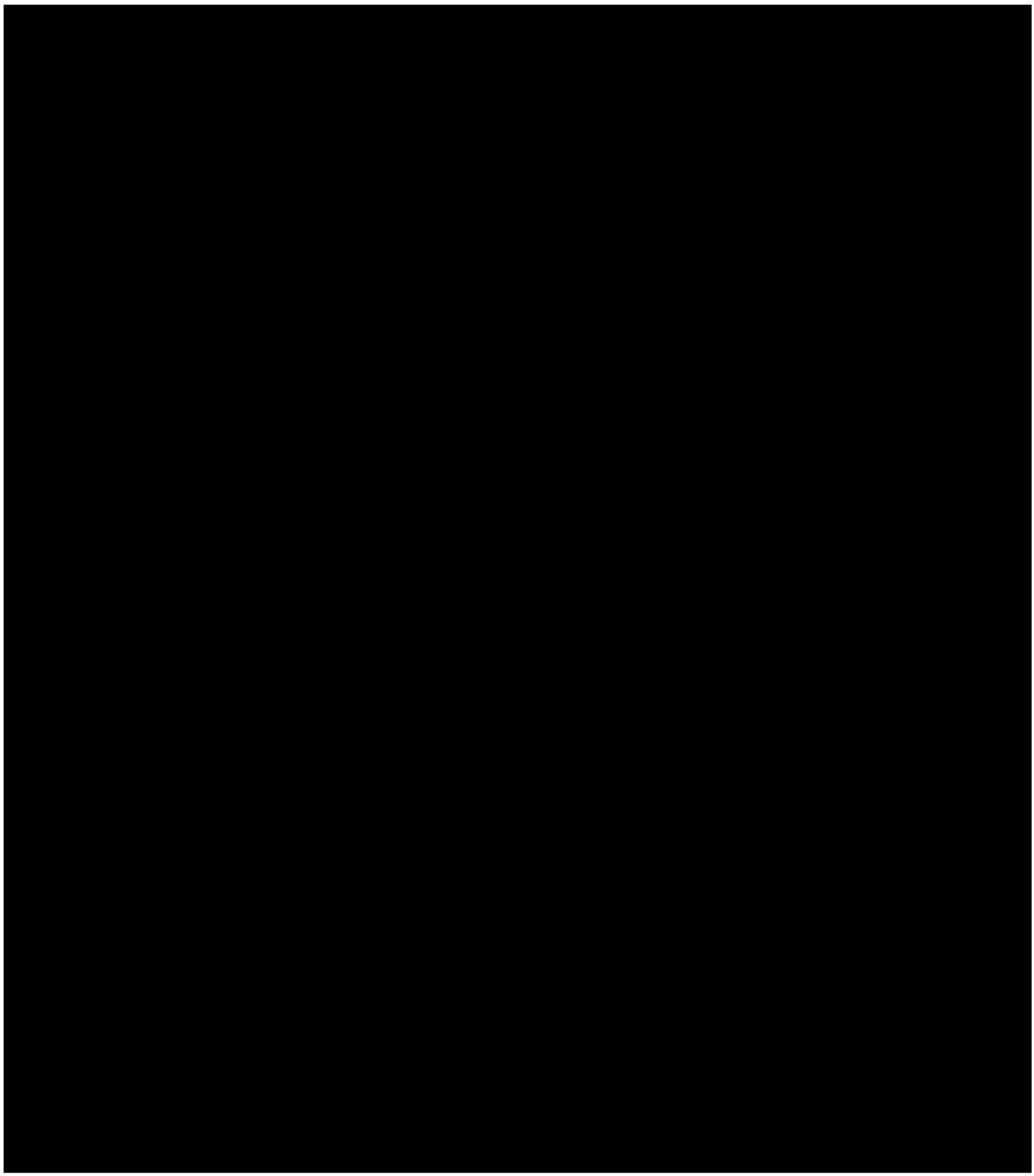


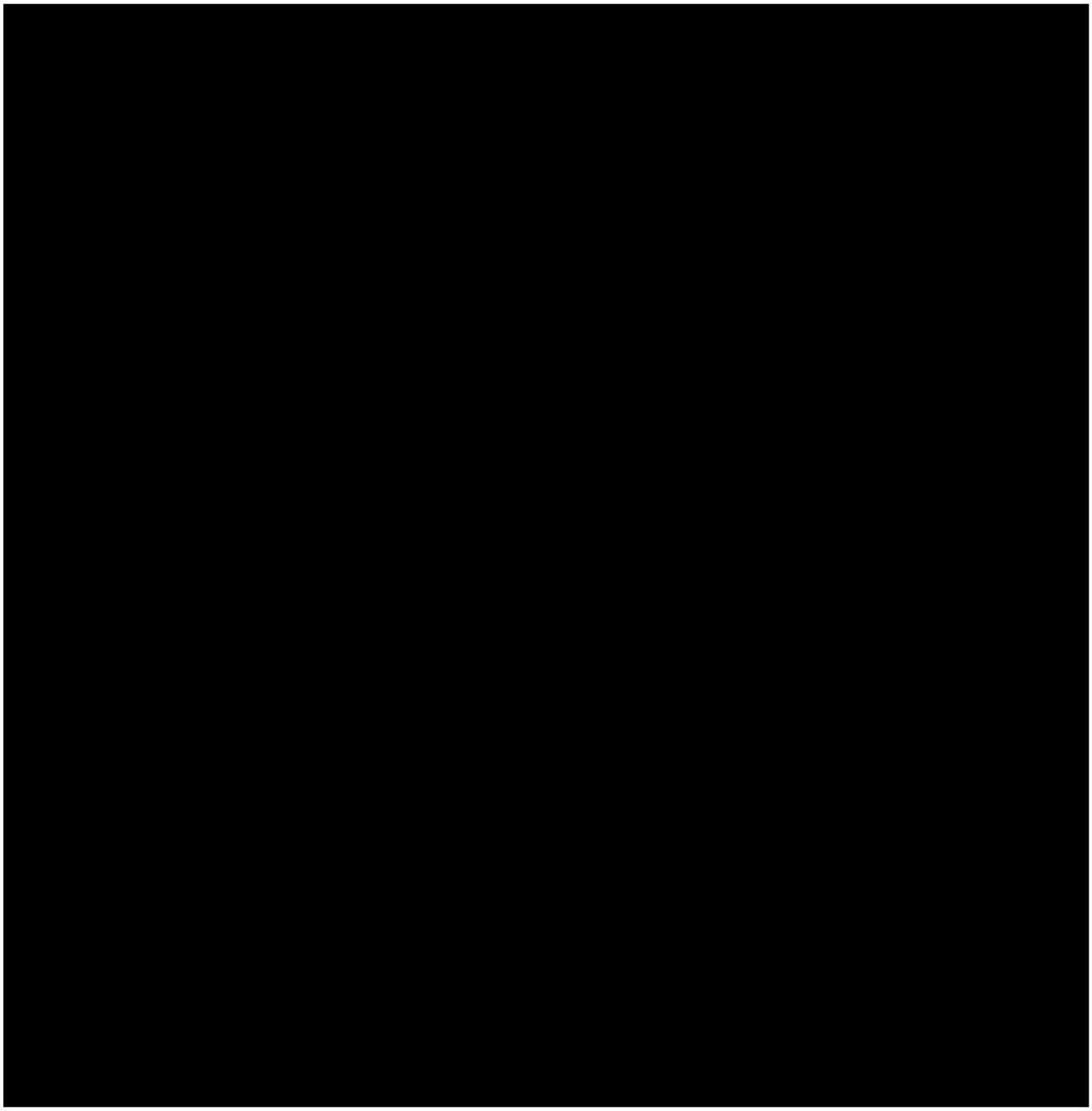


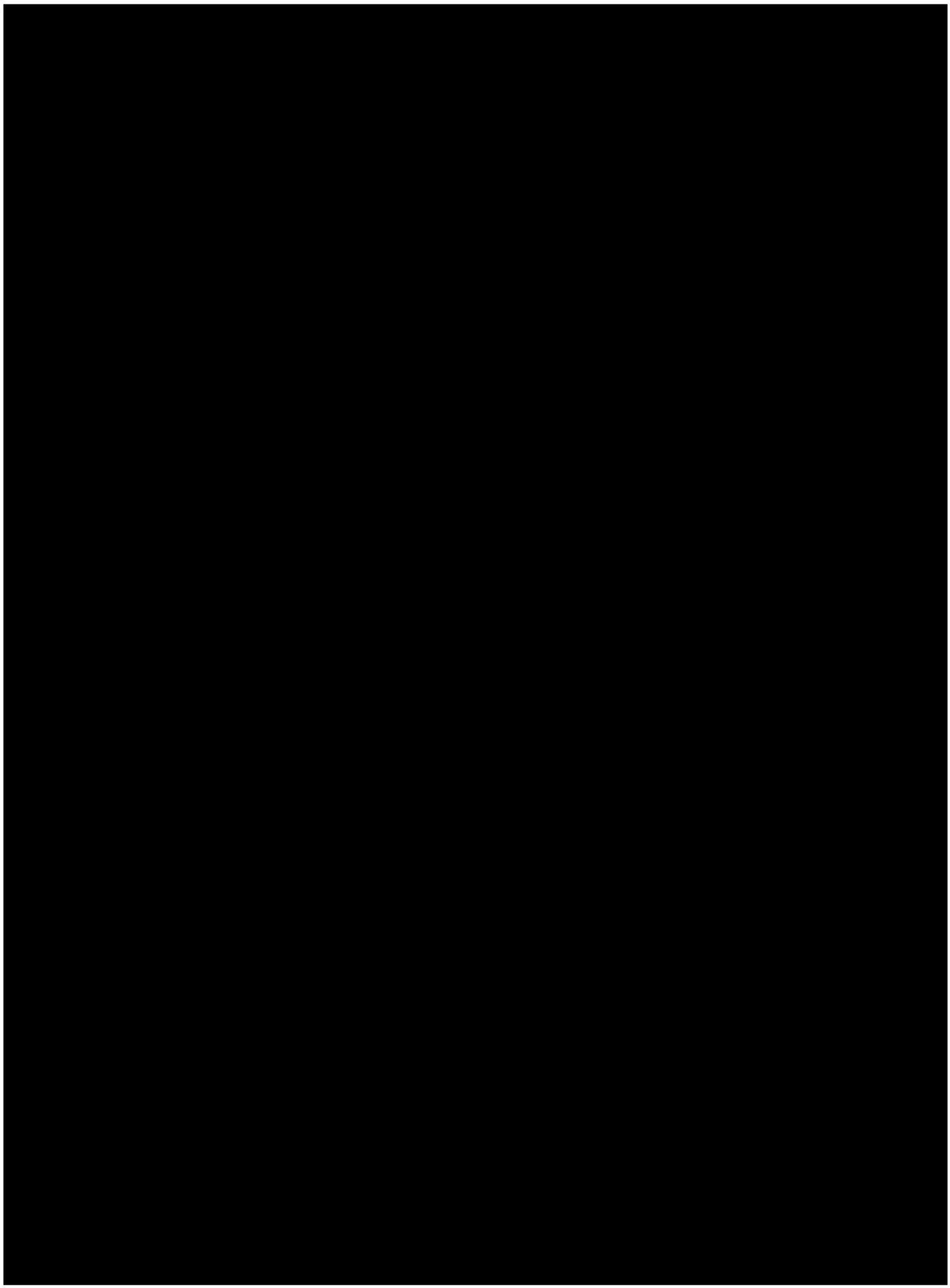


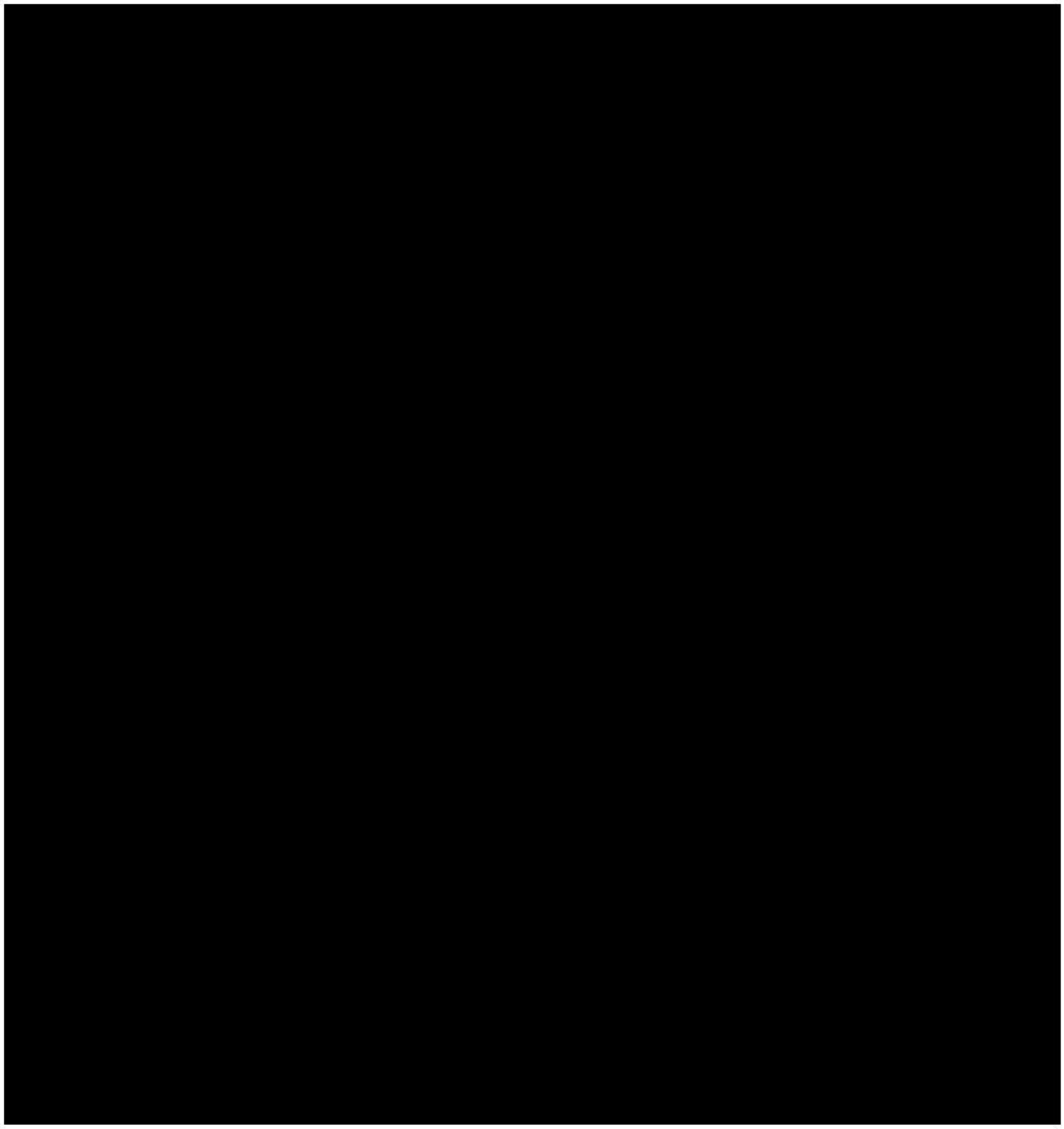
C-SSRS – Since Last Visit Version







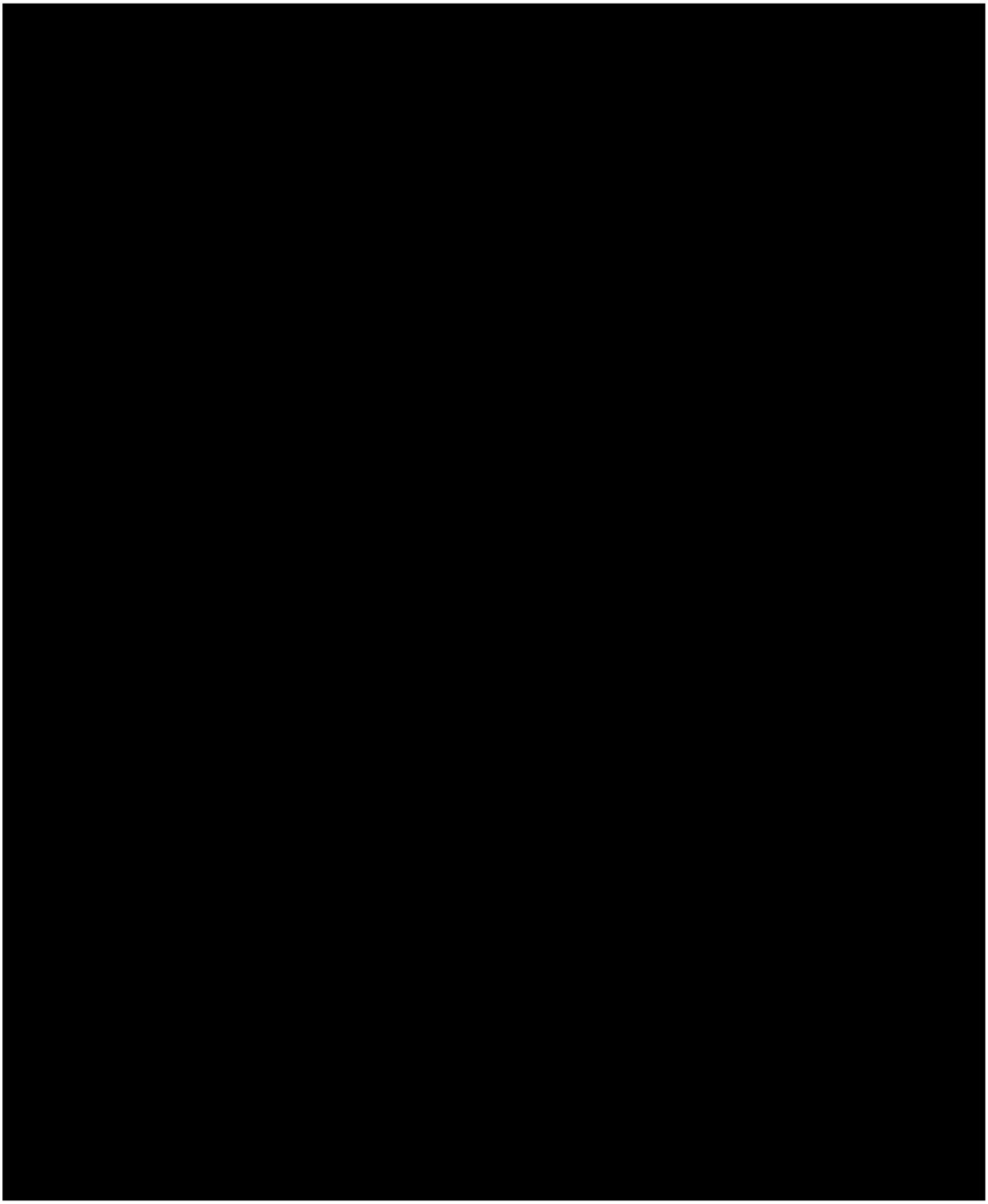


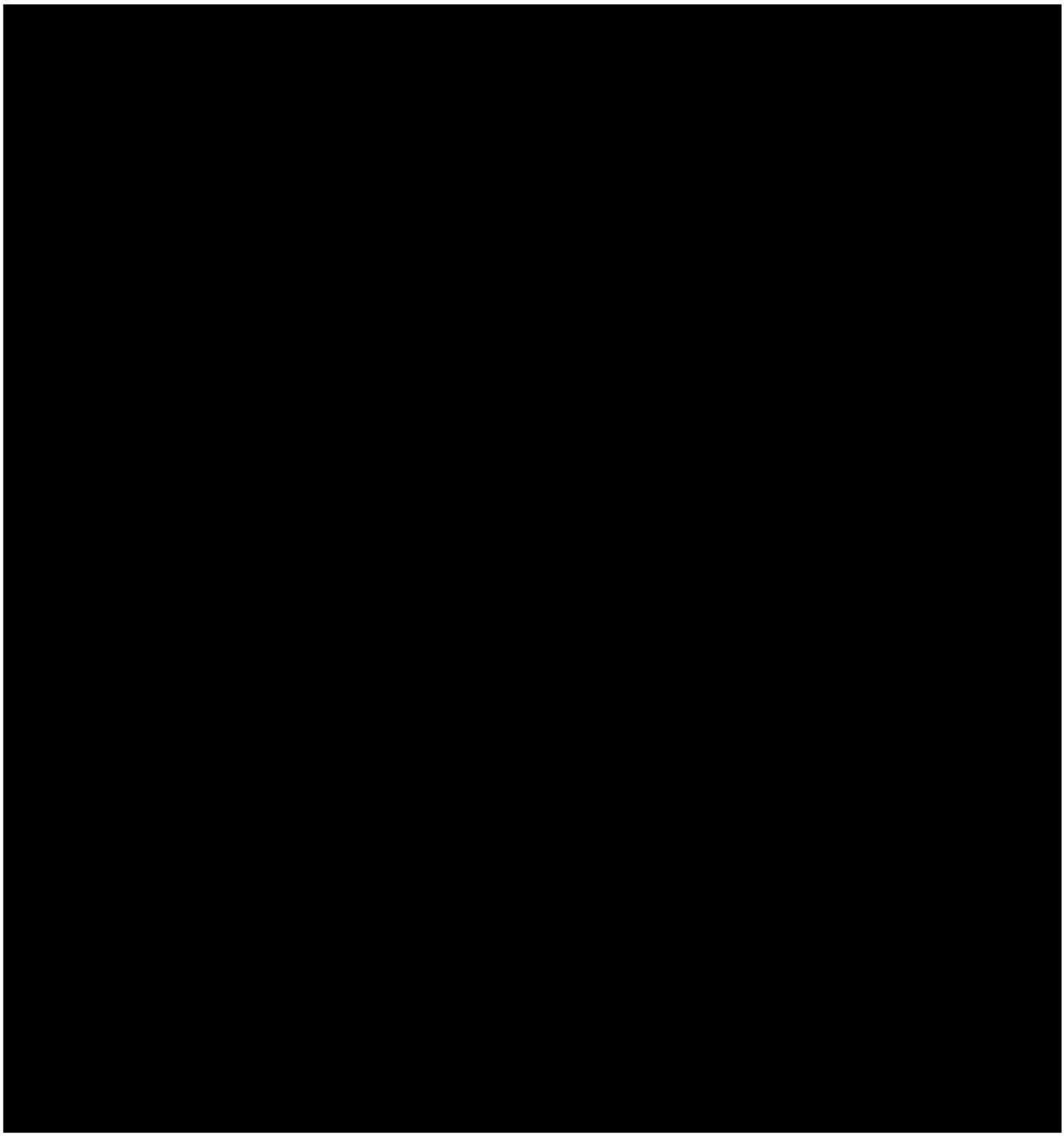


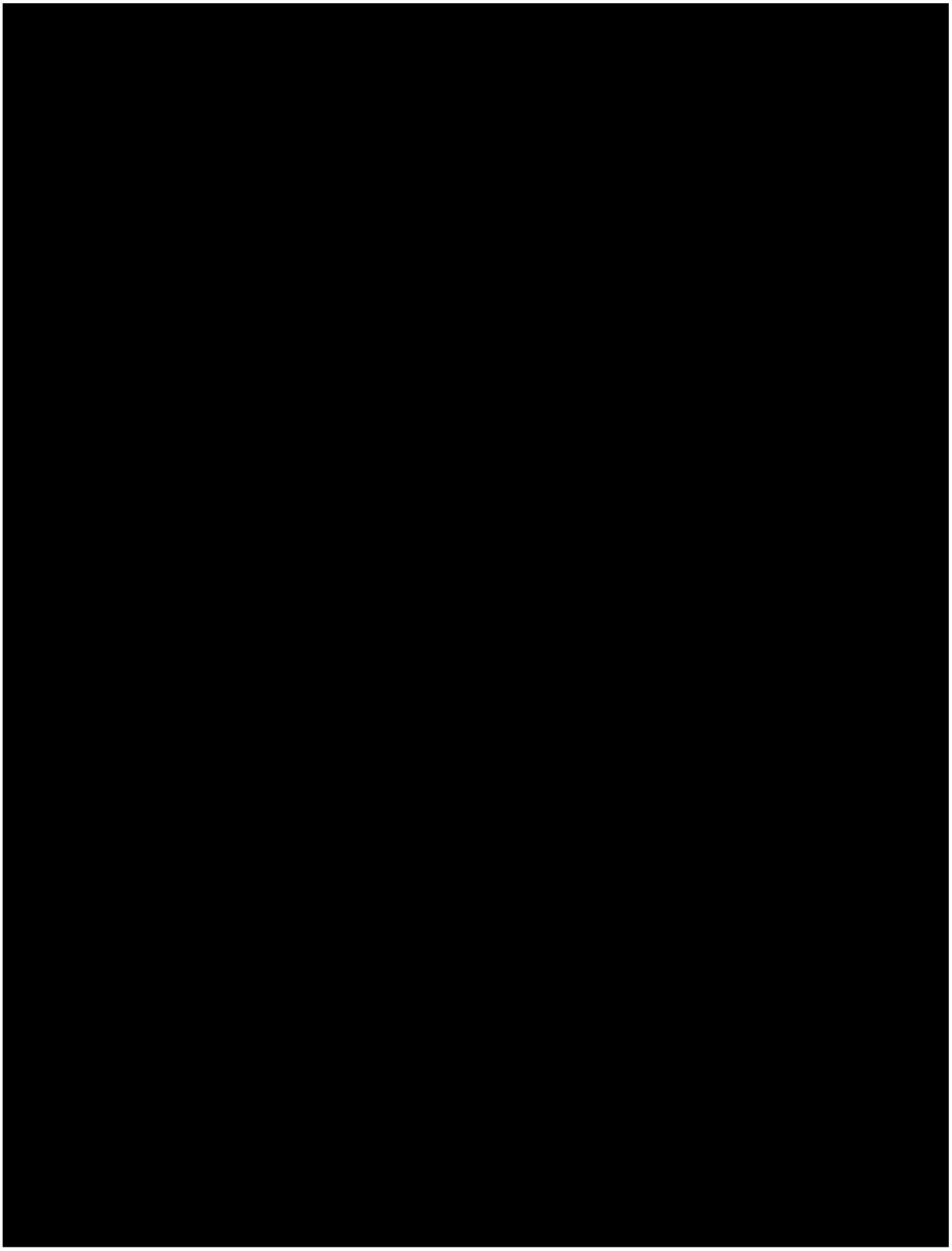
Appendix 5. Prohibited Concomitant Medication List

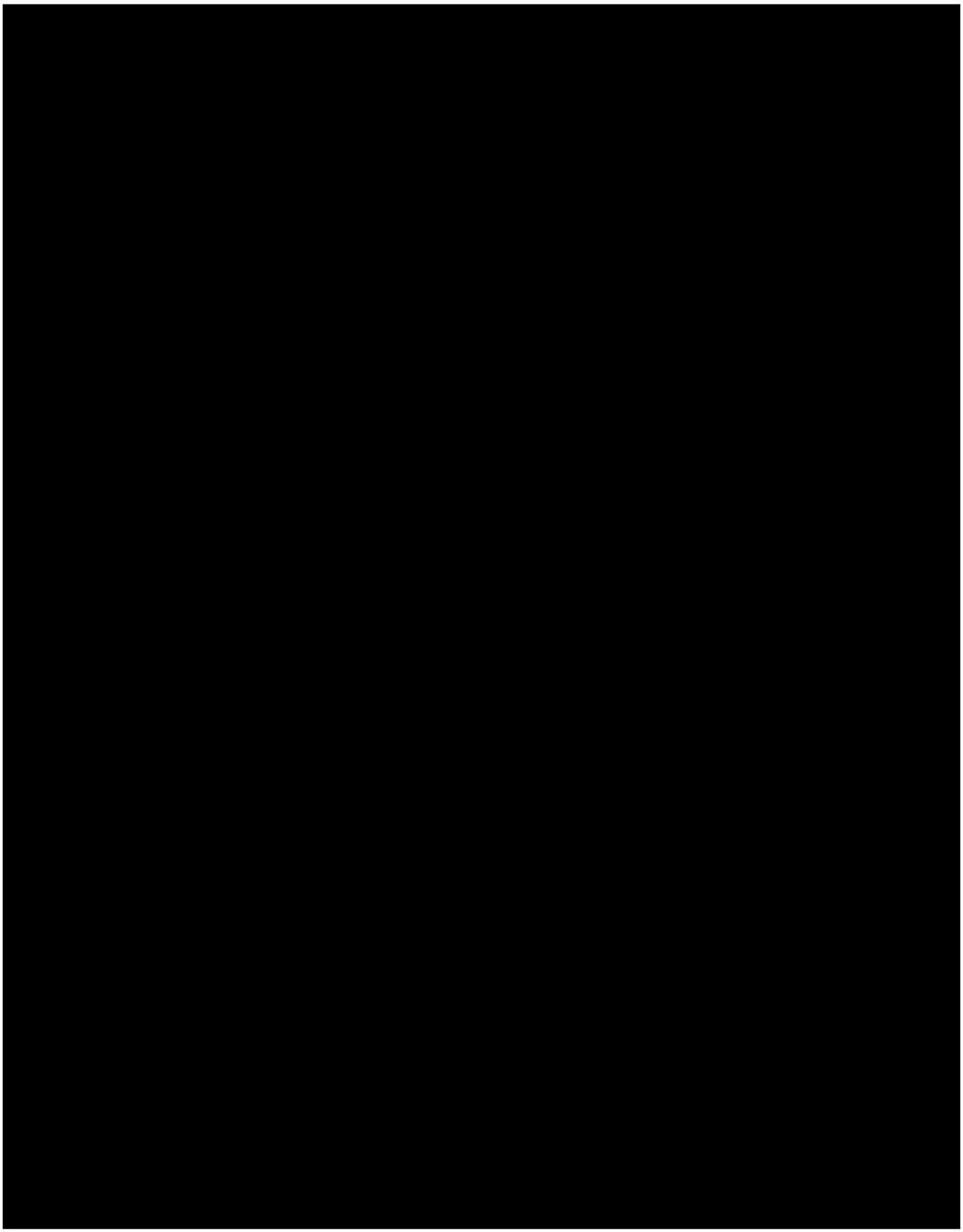
- Aminoglycoside antibiotics
- Baclofen
- Benzodiazepines for anti-spastic indication
- Botulinum toxin therapy of any serotype
- Cannabinoids
- Carisoprodol
- Chlormezanone
- Curariform drugs
- Dalfampridine
- Dantrolene
- Gabapentin for anti-spasticity indication
- Meprobamate
- Methocarbamol
- Neuroleptics
- Orphenadrine
- Cyclobenzaprine
- Tizanidine
- Tolperisone

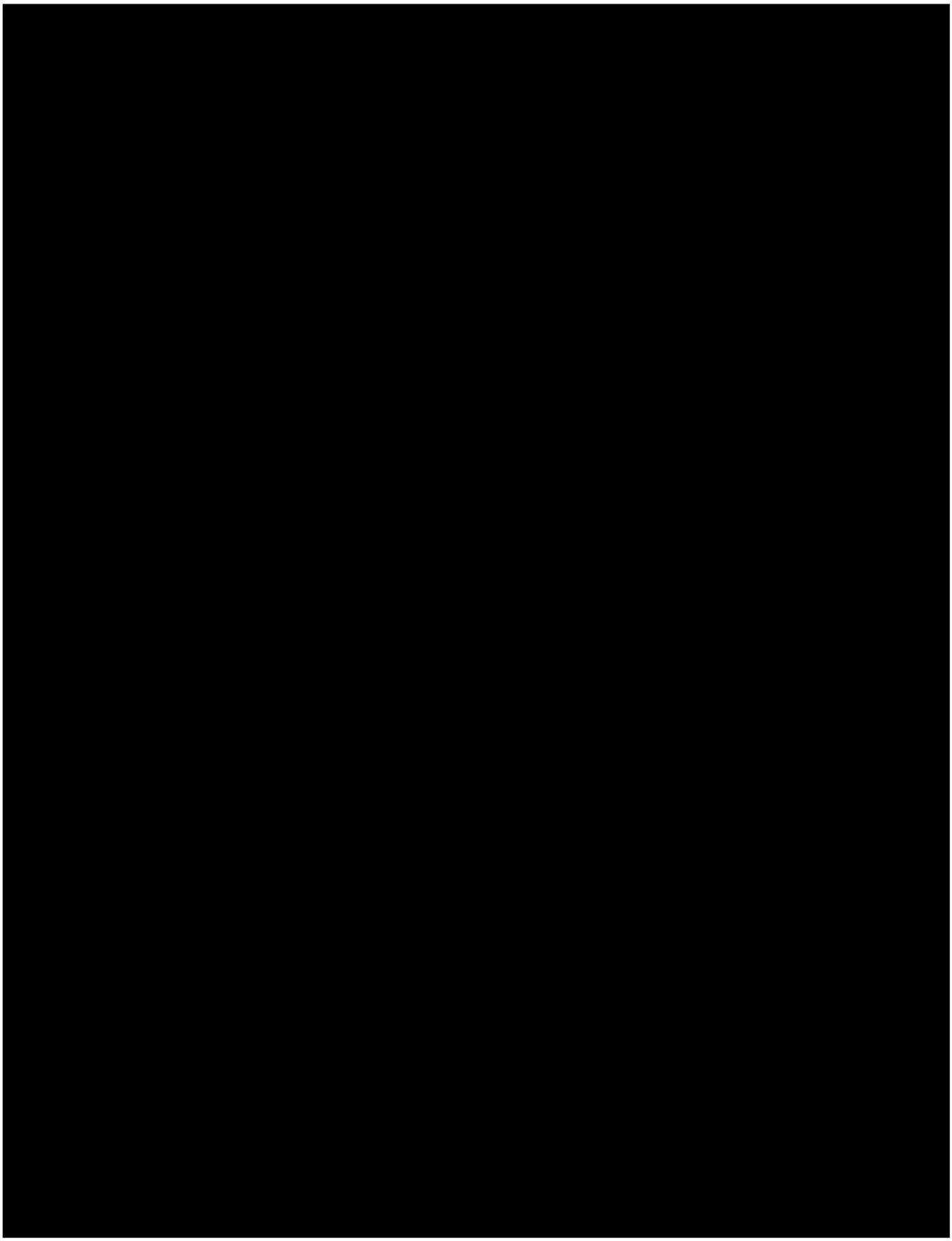
Appendix 6. Urinary Symptom Profile Questionnaire





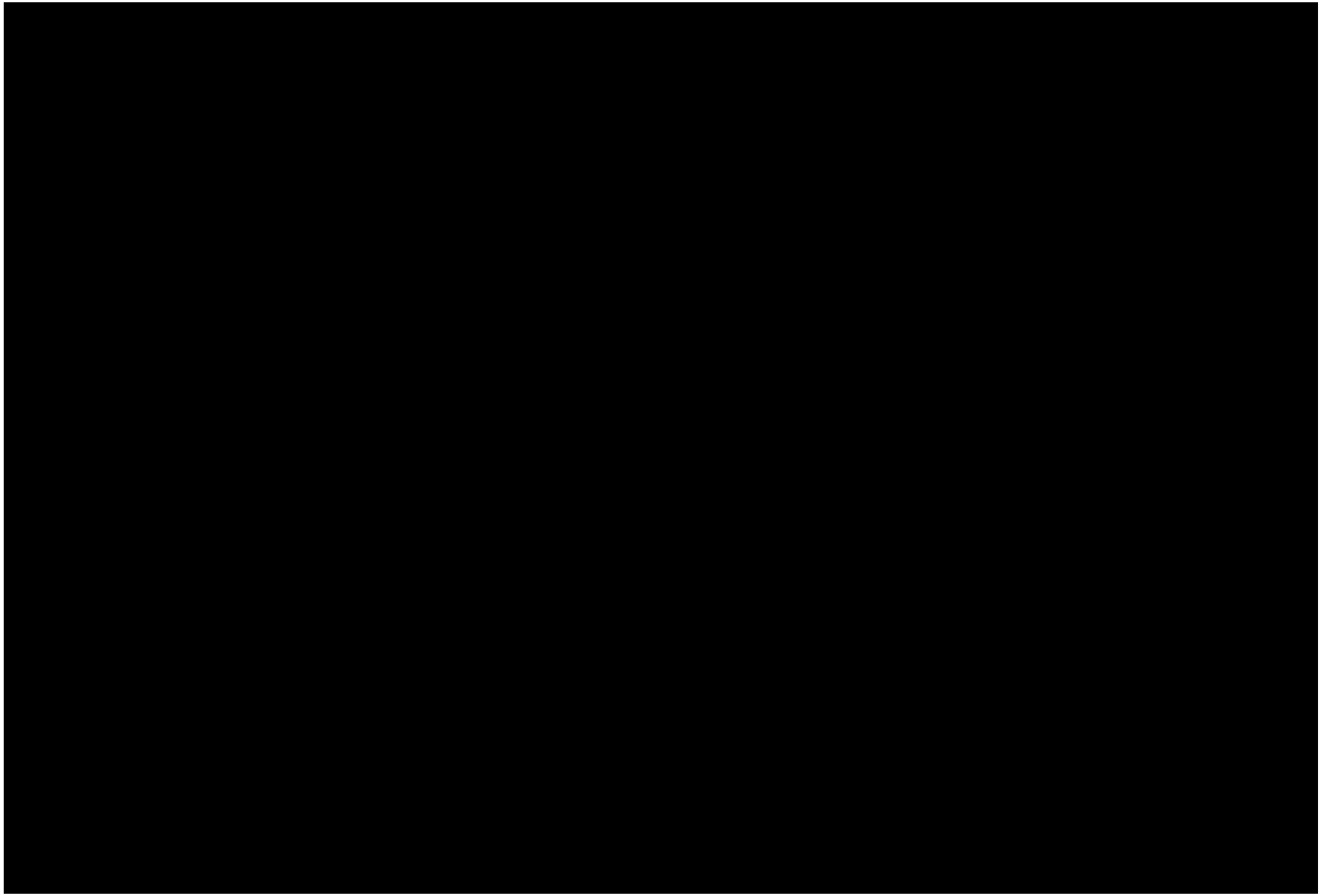


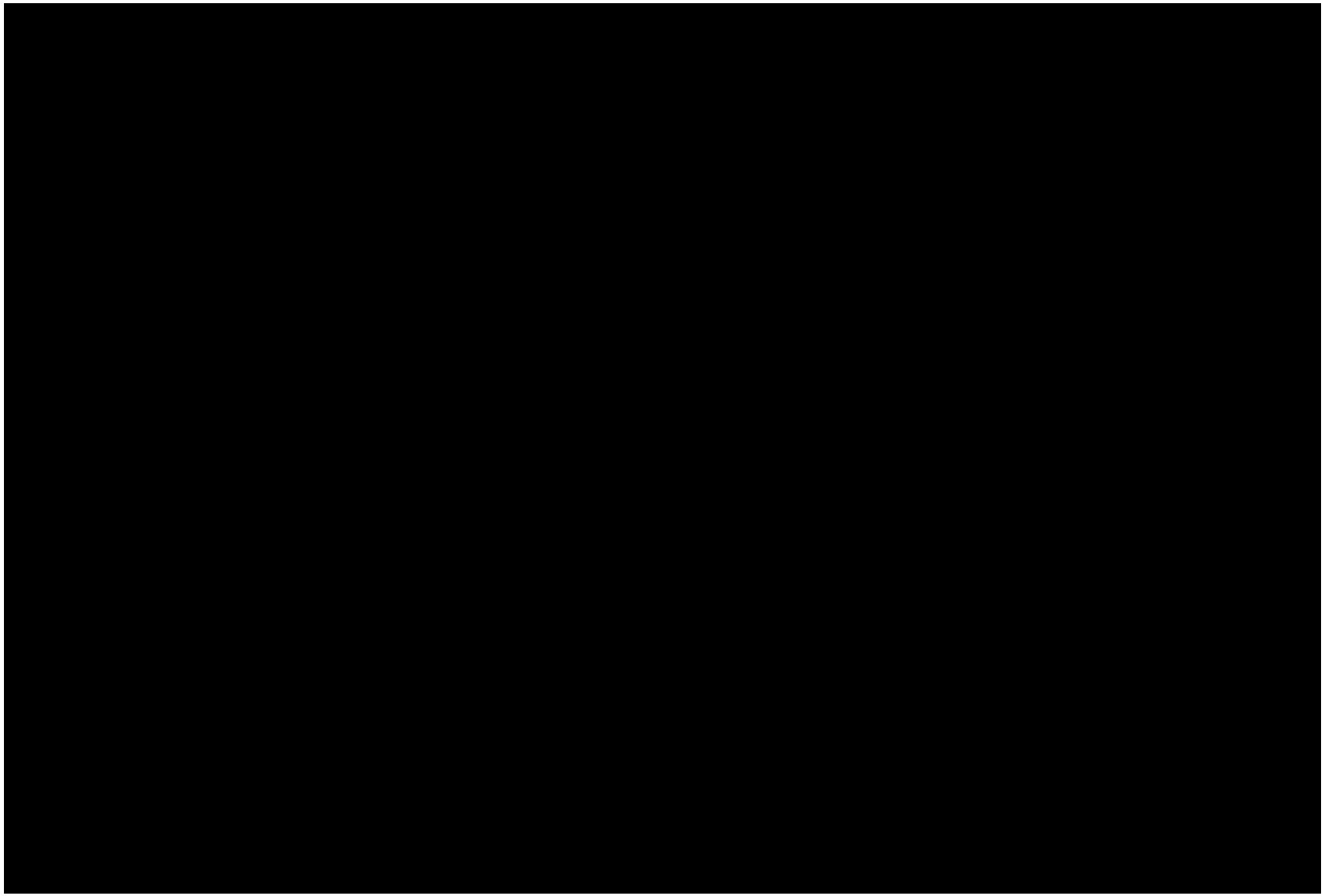




Appendix 7. [redacted]

[redacted]





Appendix 8. Summary of Changes

The following changes have been made to Protocol CLN.OS440-3005.PR.A02.USA as Country-Specific Amendment 2, applicable to the United States (US) only:

SECTION(S)	CHANGE/RATIONALE
Entire Document	Made style and editorial corrections and clarifications, fixed errors, added revised protocol number, and added hyperlinks.
Title Page	Added protocol versions history.
Sections 4.1, 5.1, 6.1 (new), 6.2, 7.7 and Table 1 footnote	Changed the Screening duration for *de novo* subjects from a minimum of 21 days to a maximum of 21 days,
Section 5.1	Added the TNmAS-MAL to the inclusion criteria for *de novo* subjects: "*De novo* subjects being considered for enrollment must have spasticity due to MS as shown by a TNmAS-MAL score ≥2."
Section 5.2	Changed exclusion criterion 12 by replacing "Baseline" with "Screening": "Subject has clinically significant abnormal laboratory values, in the opinion of the investigator at Screening (at Visit 6 for rollover subjects)."
Section 6.1 (now 6.2), Section 9, and Table 1	Moved the majority of the assessments for *de novo* subjects from Baseline to Screening: "For de novo subjects being considered for enrollment, a Screening visit should occur a maximum of 21 days prior to Baseline to allow for any concomitant medication wash-out required for Inclusion Criterion 6. For *de novo* subjects, the following procedures will be done at this Screening visit: informed consent, inclusion/exclusion criteria, withdrawal of anti-spasticity medication, demography, medical/surgical history, physical examination, height, weight, vital signs, hematology/serum chemistry/urinalysis, ECG, serum pregnancy test, C-SSRS, TNmAS-MAL, USP, EDSS, and recording of concomitant medications. For *de novo* subjects, the following assessments and procedures will be performed at the Baseline visit: assign enrollment number, vital signs, urine pregnancy test, C-SSRS, TNmAS-MAL, PGIC, USP, dispensing of study medication, recording of AEs and concomitant medications, and scheduling/confirmation of the next study visit."
Section 6.1 (now 6.2), 6.3 (now 6.4), 6.5 (now 6.6), Section 8.1, and Table 1 footnote	Removed the Patient Global Impression of Change (PGIC) at Visit 4 (Week 28).
Sections 7.1.1, 7.9, and 12.4	Changed the rule requiring subjects who miss 7 or more consecutive days of dosing to be discontinued; the new rule requires discontinuation only if the subject misses 7 or more consecutive days of dosing AND has taken less than 80% of their doses of study medication in a 42-day (6-week) period.
Sections 1 and 9.7.3	Changed name and contact information for one of the Medical Monitors for SAE reporting.
Appendix 8	Added new Appendix 8 Summary of Changes to summarize the changes made to the original protocol with Amendment 2.

The following changes have been made to Protocol CLN.OS440-3005.PR.A01 as Amendment 1:

SECTION(S)	CHANGE/RATIONALE
Entire Document	Made editorial corrections and clarifications, fixed errors, added revised protocol number, and added hyperlinks.
Title Page	Added protocol versions history.
Section 9.6.2	Corrected the mistake in the original protocol regarding a 4-point change in total USP score by replacing "A reduction of 4 points…" with "An increase of 4 points…."
Appendix 8	Added new Appendix 8 Summary of Changes to summarize the changes made to the original protocol with Amendment 1.