A PILOT STUDY OF RNS60 IN ALS

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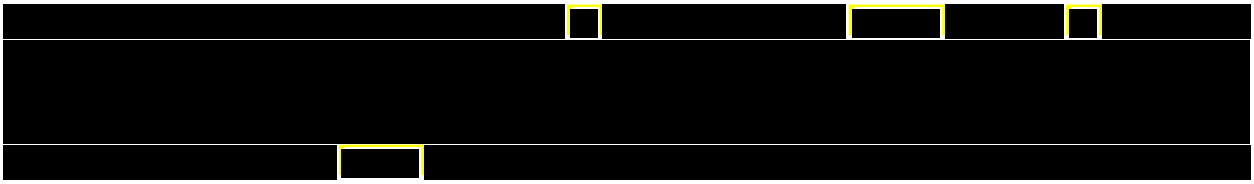


LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
API	Active Pharmaceutical Ingredient
ATLIS	Accurate Test of Limb Isometric Strength
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CSNs	Charge-stabilized nanostructures
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
EAE	Experimental autoimmune encephalomyelitis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FRAP	Ferric Reducing Antioxidant Power
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
MGH	Massachusetts General Hospital
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
N	Number (typically refers to subjects)
NDA	New Drug Application
NIH	National Institutes of Health
OHRP	Office for Human Research Protections

OHSR	Office of Human Subjects Research
PET	Positron Emission Tomography
PHI	Protected Health Information
PHRC	Partners Human Research Committee
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
ROI	Region of Interest
SAE	Serious Adverse Event/Serious Adverse Experience
SBP	Systolic Blood Pressure
SI	Site Investigator
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SVC	Slow Vital Capacity
Tregs	T regulatory cells
US	United States
VC	Vital Capacity
WOCBP	Women of Childbearing Potential

PROTOCOL SUMMARY

Study Title
A PILOT STUDY OF RNS60 IN ALS

Version Number
6.0

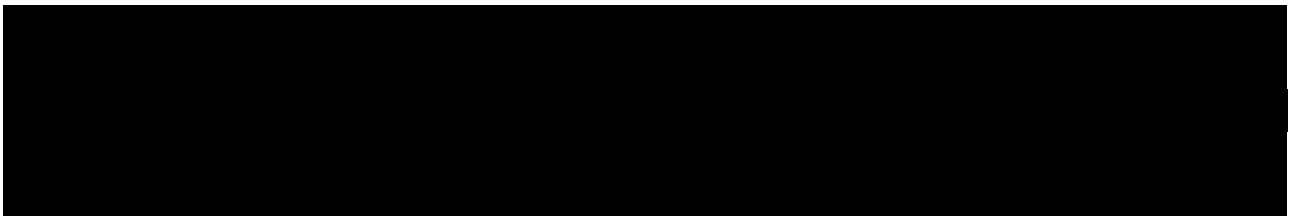
Protocol Number
RNS60-01

Study Indication
Amyotrophic Lateral Sclerosis (ALS)

Phase of Development
IIa

Rationale for the Study
Amyotrophic lateral sclerosis (ALS) is a fatal, neurodegenerative disease for which there is no cure.

A substantial body of evidence implicates the neuroimmune system and specifically activated microglia in ALS pathophysiology. Activated microglia are increased in postmortem brain and spinal cord tissue from patients with ALS compared to healthy controls, and the number of activated microglia correlates positively with faster rate of disease progression. In addition, studies of blood cells in people with ALS have shown an increased activation of two of the major inflammatory cell types in the body, monocytes and T cells. Among T cells, regulatory T cells (Tregs) have been recently proposed to play a role in ALS progression. Tregs and their FoxP3 protein expressions were reduced in rapidly progressing ALS patients and inversely correlated with progression rates. A 3.5-year prospective study revealed that early reduced FoxP3 levels were predictive of future rapid progression and attenuated survival. These data suggest that Tregs may influence disease progression rates in ALS.



[redacted]

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Study Design

This is a single center, open label, pilot trial of RNS60 in people with ALS. Study participants will receive study drug for 24 weeks following the core study schedule of activities. Upon nearing completion of the core study, subjects will be given the option to continue to receive drug for approximately an additional 24 weeks, for a total of approximately 48 weeks on study drug, following the optional extension phase schedule of activities.

Study Objectives and Endpoints

The primary objectives of the study are to determine the preliminary safety and tolerability of RNS60 treatment in 18 people with ALS over 24 weeks. We will measure the impact of RNS60 on blood biomarkers of inflammation. In addition, in a subgroup of 13 study participants ("Imaging group"), an additional primary objective is to measure the impact of RNS60 on [^{11}C]-PBR28 uptake in the motor cortices and brain stem measured by positron emission tomography (PET) imaging.

We will also measure the effect of RNS60 on ALS clinical outcomes [ALS functional rating scale (ALSFRS-R), slow vital capacity (SVC), strength (measured by ATLIS- Accurate Test of Limb Isometric Strength)].

For participants who elect to continue with the optional 24 week extension, safety parameters (labs, EKG, adverse events, C-SSRS) will continue to be monitored. We will also collect ALSFRS-R and SVC outcome measures.

Study Location

Massachusetts General Hospital (MGH)

Number of Planned Subjects

Up to 25 subjects will be screened for the study with the goal of enrolling 18 for treatment. All 18 enrolled subjects will be given an opportunity to sign a consent form addendum during Weeks 18-22 to receive approximately 24 additional weeks of drug treatment.

Study Population

This study will be conducted in subjects who meet the El Escorial criteria of possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS. At screening, eligible subjects must be at least 18 years old and must provide written informed consent prior to screening. Subjects on a stable dose of riluzole and those not taking riluzole, and women of child-bearing age at screening are eligible for inclusion as long as they meet specific protocol requirements. Safety, tolerability, blood biomarkers, and clinical outcomes will be collected on all subjects. In a subgroup of 10 study participants ("Imaging group") neuro-imaging will be performed. Detailed criteria are described in the body of the protocol.

Treatment Plan

RNS60 will be administered in two ways: by intravenous (IV) infusion one day a week (infusion dose: 375ml, infused over a 40-min period) and by inhalation (the remaining 6 days a week, 4 ml/day) for 24 weeks or up to approximately 48 weeks.

Duration of Treatment and Follow-up

Subjects will remain on treatment in the core study for 24 weeks. Each subject will also have a Week 28 Follow-up Telephone Interview to assess for adverse events (AEs), changes in concomitant medications and to administer the ALSFRS-R. After the completion of the trial, subjects will be called by phone approximately every 3 months to ascertain ALSFRS-R and vital status for up to 2 years.

Optional Extension Phase

Upon nearing completion of the core study, subjects will be given the option to continue RNS60 treatment for an additional 24 weeks of weekly infusions and daily inhalations. Subjects interested in continuing treatment in the extension phase will sign an additional IRB-approved consent addendum document with the physician-investigator during a clinic visit between Week 18 and Week 23. Extension phase drug dispensing will occur at the Week 23 visit. Safety parameters such as blood work, urine samples, EKGs, and adverse event recording will continue to be monitored during the extension phase. ALSFRS-R and SVC outcome measures will be collected at two time points. Each subject will also have a Week 52 Follow-up Telephone Interview to assess for adverse events (AEs), changes in concomitant medications and to administer the ALSFRS-R. After the completion of the trial, subjects will be called by phone approximately every 3 months to ascertain ALSFRS-R and vital status for up to 2 years.

Subjects may choose to discontinue RNS60 treatment at any point during the optional extension phase.

SCHEDULE OF ACTIVITES – CORE STUDY

	Screening Visit[1]	Baseline Visit	Weekly visits Week 1 through Week 10	Wk 11 Visit	Weekly visits Week 12 through Week 22	Week 23 Visit	Week 28 Phone call	Follow Up Chart Review / Phone Call[2]	Final Safety Visit (for early study drug discontinuation only)[3]
Visit Window	**-42 days**	**Day 0**	**Day 7 ± 3**	**Day 77 ± 3**	**Day 84 ± 3**	**Day 161 ± 3**	**Day 196 + 5**	**Every 3 months**	
Informed Consent	X								
Eligibility Criteria	X	X							
Demographics	X								
ALS History / ALS Diagnosis	X								
Medical History	X								
Blood sample for TSPO Affinity test†	X								
12-lead ECG	X	X				X			X
Safety Labs[4]	X	X		X		X			X
Vital Signs /Height and weight[5]	X	X	X	X	X	X			X
Neurological exam	X					X			X
Physical exam	X					X			X
[^{11}C]PBR28-PET†		X*			X**				
ALSFRS-R		X*		X	X**	X	X	X	X
U Penn Upper Motor Neuron Burden[6]	X	X		X		X			X
Slow Vital Capacity		X*		X	X**	X		X	X
Strength measurement (ATLIS)[7]	X	X		X		X			X
C-SSRS		X		X		X			X
RNS60 infusion		X	X	X	X	X			
RNS60 Dispensing (for inhalation)		X	X (week 7)		X (week 15)				
RNS60 Accountability			X	X	X	X			X
AE review[8]	X	X	X	X	X	X	X		X
Concomitant Meds	X	X	X	X	X	X	X		X
Collection of blood biomarkers		X		X		X			X

[1] Screening procedures must be completed within 6 weeks prior to Baseline Visit.

[2] Follow-up will continue every 3 months up to 2 years to collect data on SVC, ALSFRS-R, and survival status. This information may be obtained via chart review and patient contact.
[3] Follow-up phone call to occur 28 +5 days after the last dose of study drug if a subject discontinues from the study prematurely.
[4] Safety labs include Hematology (CBC with differential), Complete Chemistry Panel, Liver Function Tests, Urinalysis, Urine pregnancy test (WOCBP).
[5] Vital signs include systolic and diastolic pressure in mmHg, respiratory rate/minute, heart rate/minute, temperature and weight. Height measured at Screening Visit only.
[6] The Penn Upper Moter Neuron-Burden (UMN-B) includes testing of reflexes, the CNS Lability Scale (CNS-LS) and the Ashworth Spasticity Scale.
[7] If time permits, ATLIS will be performed at the screening visit.
[8] Adverse events that occur AFTER signing the informed consent form will be recorded.
**Off* treatment [^{11}C]PBR28-PET will be performed one time only between the Screening and Baseline visit. ALSFRS-R and SVC will be repeated on the day of the scan.
***On* treatment [^{11}C]PBR28-PET will be performed one time only between the Week 18 and Week 23 visits. ALSFRS-R and SVC will be assessed the day of the scan ONLY.
†For subjects in the "Imaging group" only.

SCHEDULE OF ACTIVITES – OPTIONAL EXTENSION PHASE

	Weekly visits Week 24 through Week 34	Week 35	Weekly visits Week 36 through Week 46	Week 47	Week 52 Phone Call	Follow Up Chart Review / Phone Call[2]	Final Safety Visit (for early study drug discontinuation only)[1]
Visit Window	Day 168 ± 3	Day 245 ± 3	Day 252 ± 3	Day 329 ± 3	Day 364 ± 3	Every 3 months	
12-lead ECG		X		X			X
Safety Labs[3]		X		X			X
Vital Signs / Weight[4]	X	X	X	X			X
Neurological exam				X			X
Physical exam				X			X
ALSFRS-R		X		X	X	X	X
Slow Vital Capacity		X		X		X	X
C-SSRS		X		X			X
RNS60 infusion	X	X	X	X			
RNS60 Dispensing (for inhalation)	X (week 30)		X (week 38)				
RNS60 Accountability	X	X	X	X			X
AE review[3]	X	X	X	X	X		X
Concomitant Meds	X	X	X	X	X		X

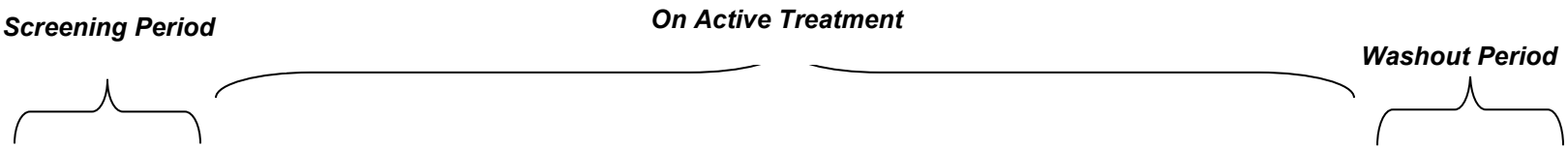
[1] Follow-up phone call to occur 28 ± 5 days after the last dose of study drug if a subject discontinues from the study prematurely.

[2] Follow-up will continue every 3 months up to 2 years to collect data on SVC, ALSFRS-R, and survival status. This information may be obtained via chart review and patient contact.

[3] Safety labs include Hematology (CBC with differential), Complete Chemistry Panel, Liver Function Tests, Urinalysis, Urine pregnancy test (WOCBP).

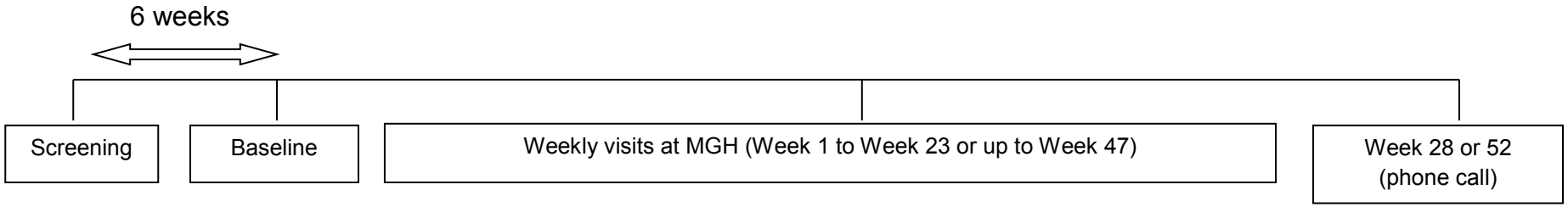
[4] Vital signs include systolic and diastolic pressure in mmHg, respiratory rate/minute, heart rate/minute, temperature and weight.

STUDY WORKFLOW



~ 25 Screened

18 Subjects on RNS60; drug is administered by weekly IV infusions (infusions to occur at MGH) as well as by intranasal administration the remaining 6 days a week.



Subjects who discontinue from the study early will be asked to return to the study site for Final Safety assessments, and will be asked to have a final Follow-Up Telephone Call 28 days (+5 days) after taking their last dose of study drug.

1 ETHICS/PROTECTION OF HUMAN SUBJECTS

1.1 Institutional Review Board (IRB)

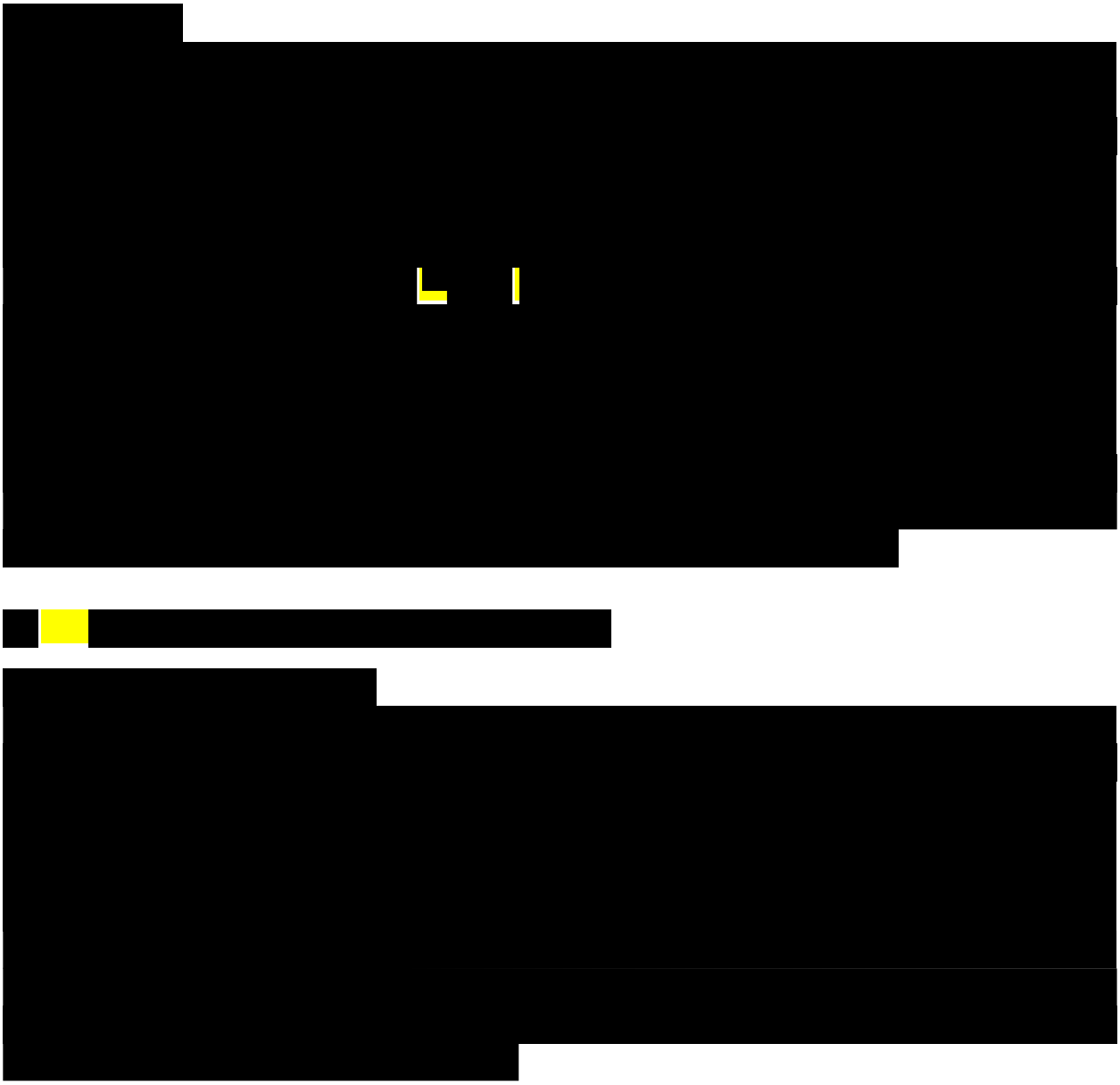
This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to IRBs.

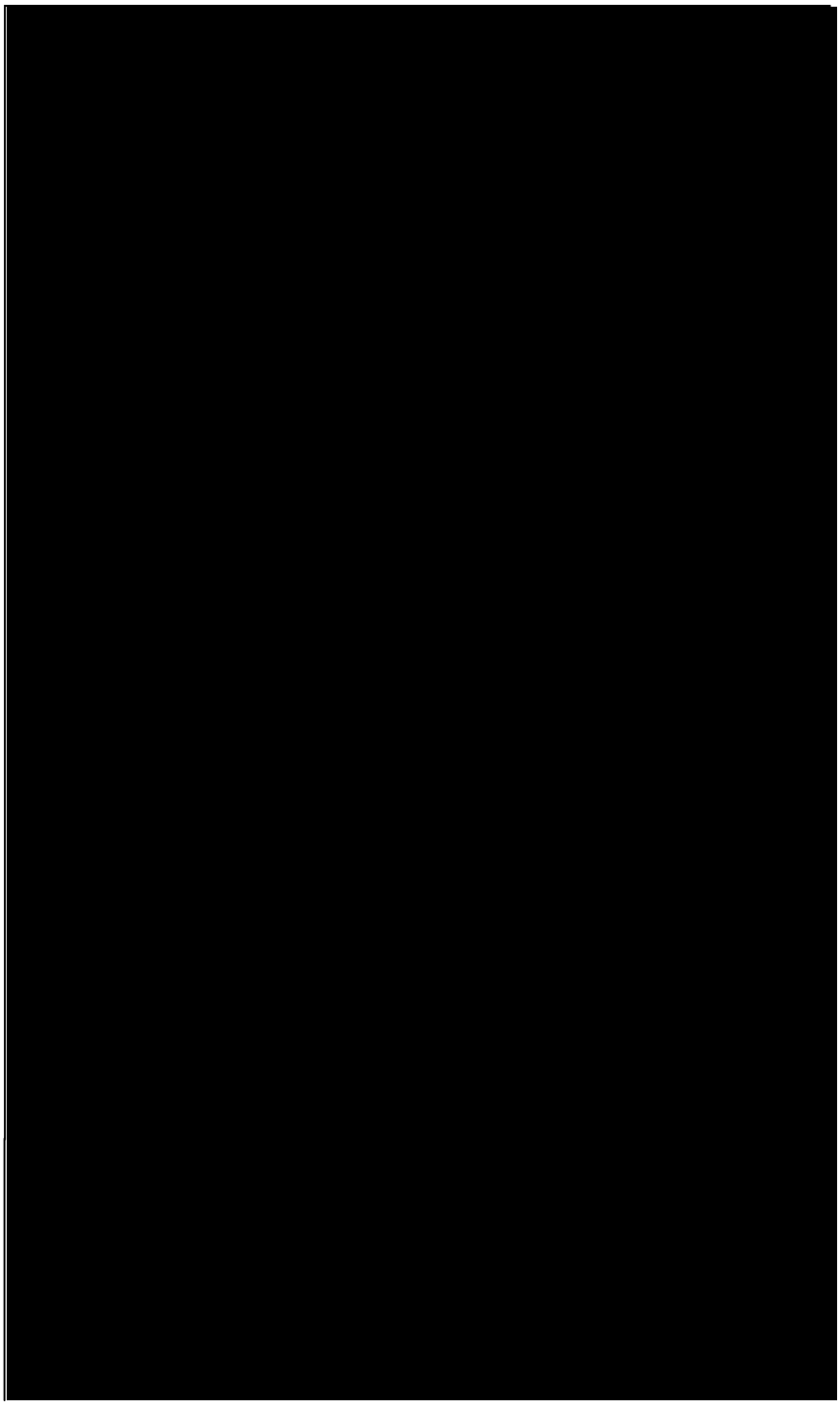
1.2 Ethical Conduct of Study

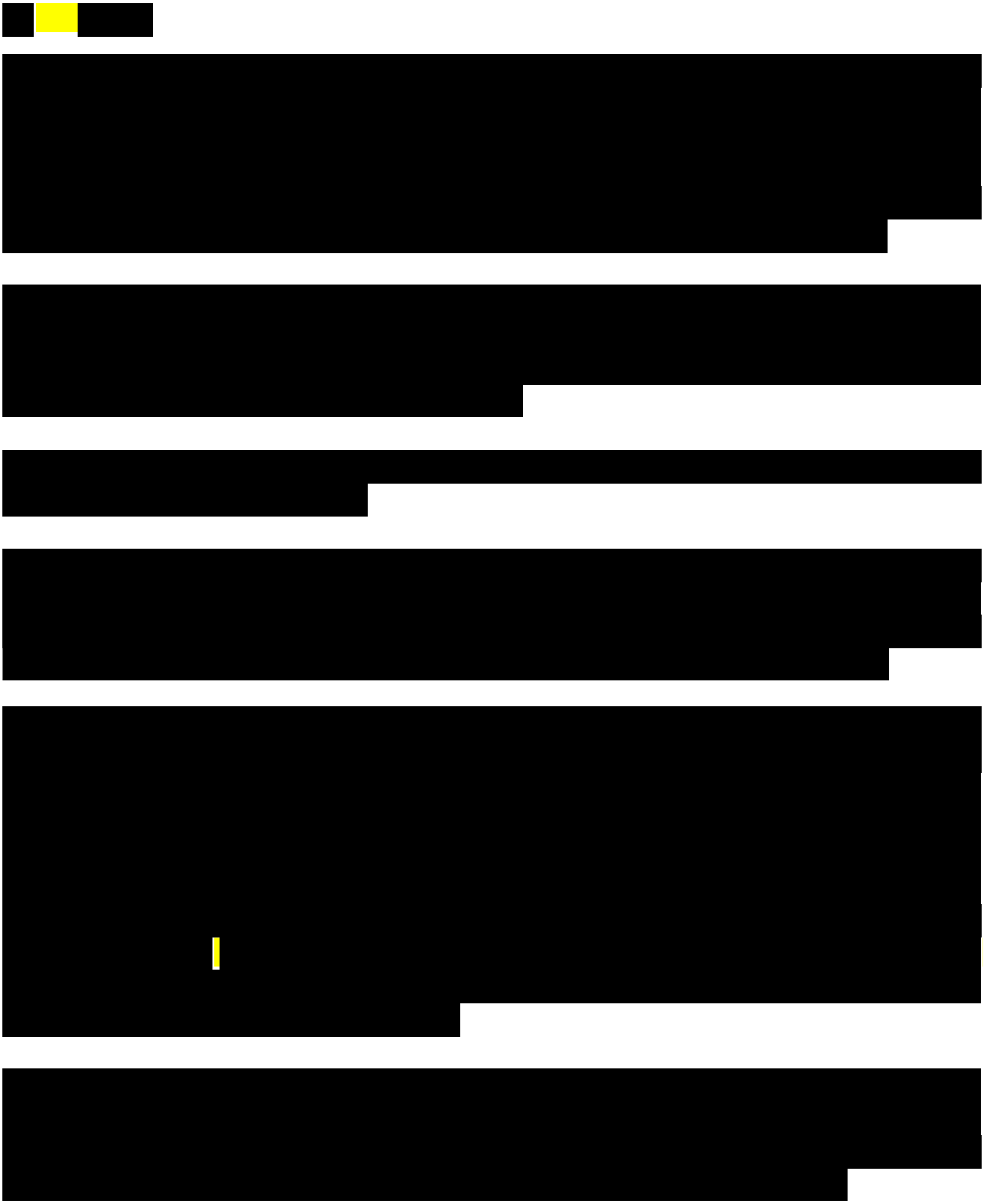
The study will be conducted in accordance with GCP defined by the International Conference on Harmonization (ICH) and the ethical principles of the Declaration of Helsinki.

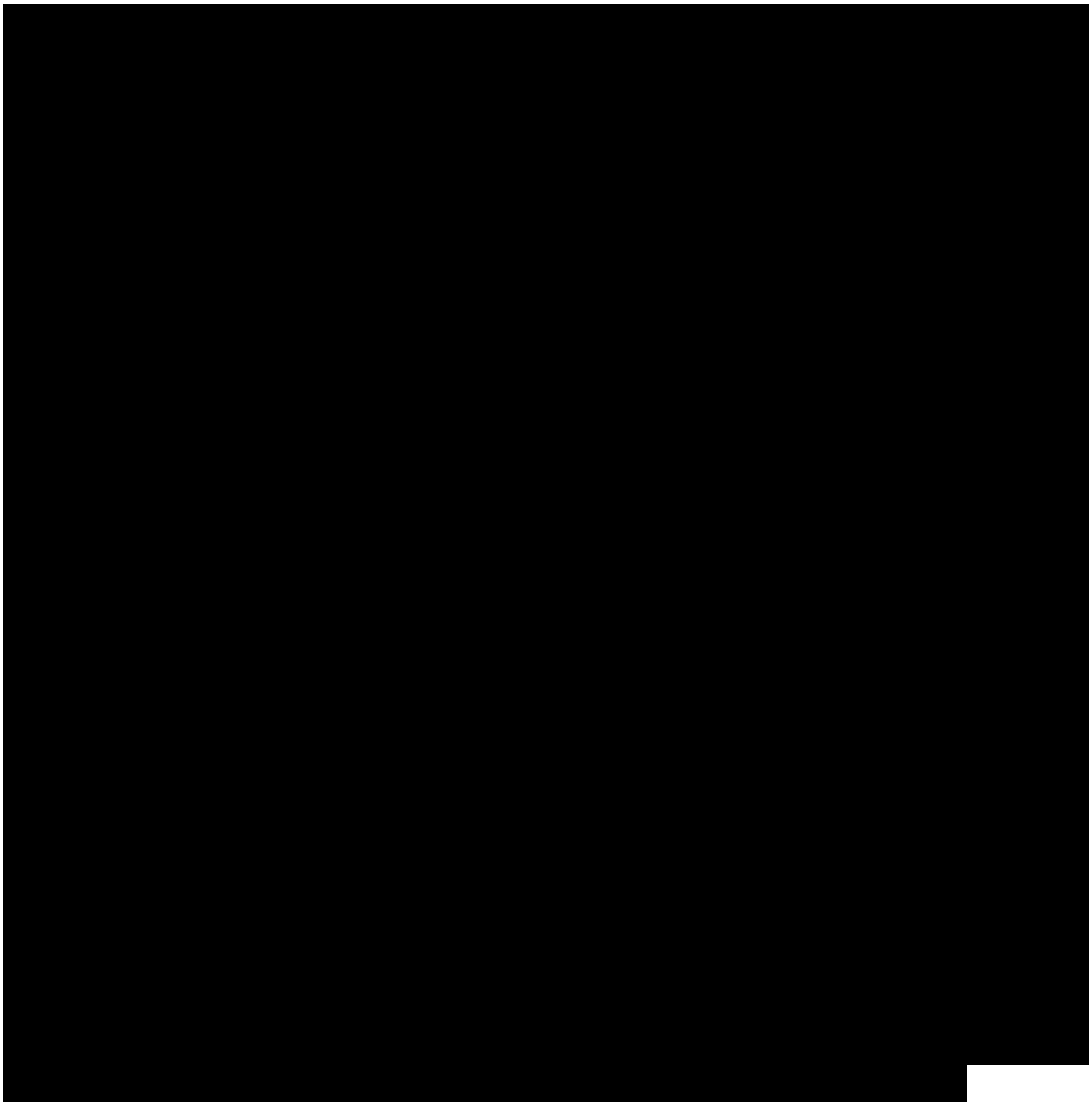
1.3 Subject Information and Consent

This study will be conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations (CFR), Federal Regulations and ICH Guidance Documents pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, subjects will be informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. Subjects will be given adequate time to ask questions and become familiar with the study prior to providing consent to participate. Subjects will give their written consent to participate in the study and will be provided with a copy of the fully executed consent form for their records.









3 OBJECTIVES

3.1 Study Objectives

The primary objectives of the study are to determine the safety and tolerability of RNS60 in 18 patients with ALS. The following clinical outcomes will be collected: ALS functional rating scale (ALSFRS-R), slow vital capacity (SVC), strength (measured by ATLIS- Accurate Test of Limb Isometric Strength). An additional primary objective is to measure the impact of RNS60 on several markers of neuro-inflammation measured by blood biomarkers in all subjects and by [^{11}C]-PBR28 positron emission tomography (PET) imaging in a subgroup of 13 subjects.

3.2 Study Outcome Measures

For all subjects enrolled in the study, the following will be primary outcome measures:

1- Safety, as measured by AEs and clinically meaningful changes in vital signs, physical examination, and standard clinical laboratory tests;
2- Tolerability, defined as the ability of subjects to complete the entire 24-week treatment portion of study;
3- Clinical outcomes: Measured by ALSFRS-R, SVC, and strength (measured by ATLIS).
4- Blood biomarkers of inflammation.

For subjects in the "Imaging group", the following additional outcome measures will be obtained:

1- Neuroimaging biomarkers ([^{11}C]-PBR28-PET) including both regions of interest (ROI) and voxel-based analyses

4 STUDY DESIGN

4.1 Overall Study Design and Plan

During the enrollment period, approximately 25 subjects will be screened at the Massachusetts General Hospital (MGH). Approximately 18 of these subjects are expected to be eligible to receive RNS60 per study protocol. RNS60 will be administered in two ways: by IV infusion one day a week (infusions to occur at MGH) and by inhalation (once a day for the remaining 6 days a week). All visit windows (± 3 days) are consecutive calendar days and are calculated from the day the participant starts study treatment (the day of the Baseline Visit).

4.2 Study Centers

This study will be conducted as a single center study at the MGH.

4.3 Study Duration

Subjects in the core study will remain on treatment for 24 weeks. Subjects may elect to continue with the 24-week extension phase sometime between Week 18 and Week 23. Each subject will also have a Follow-up Telephone Interview 28 days ±5 to assess for AEs, changes in concomitant medications and to administer the ALSFRS-R.

4.4 Protocol Adherence

The Principal Investigators (PIs) agree to adhere to the protocol detailed in this document and agrees that any changes to the protocol must be approved by the site Institutional Review Board (IRB). The PIs will be responsible for enrolling only those study subjects who have met protocol eligibility criteria.

5 SELECTION AND WITHDRAWAL OF STUDY POPULATION

5.1 Number of Study Subjects

Approximately 25 subjects will be consented for the study. Any subject who signs consent will be considered enrolled in the study. Screening study procedures will begin after informed consent.

If a subject fails screening, at a minimum, the following information will be captured and entered in the data capture system: inclusion/exclusion criteria, demographics, screening lab results, reason for screen failure.

Fifteen (15) subjects will receive RNS60 for up to 48 weeks per study protocol and will be followed up to 52 weeks.

5.2 Inclusion and Exclusion Criteria

5.2.1 Inclusion Criteria

Study subjects meeting all of the following criteria will be allowed to enroll in the study:

1- ALS volunteers must be diagnosed as having possible, probable, probable-laboratory supported, or definite ALS, either sporadic or familial according to modified El Escorial criteria.
2- Age 18-80, able to provide informed consent, and comply with study procedures.
3- Participants must not have taken riluzole for at least 30 days, or be on a stable dose of riluzole for at least 30 days, prior to screening (riluzole-naïve participants are permitted in the study).
4- Women must not be lactating or able to become pregnant (e.g. post menopausal, surgically sterile, or using adequate birth control) for the duration of the study and 3 months after study completion.
5- Males should practice contraception for the duration of the study and 3 months after completion.

Study subjects in the "Imaging group" will also need to meet the following additional inclusion criteria:

1- Ability to safely lie flat for 90 min for PET procedures in the opinion of the study physician.
2- High or mixed affinity to bind TSPO protein (Ala/Ala or Ala/Thr) (Details below).
3- Score of 25 or greater (out of 45) on the Upper Motor Neuron Burden (Details below).

TSPO affinity test*:* venous blood will be drawn from all participants at Screening in order to have them genotyped for the Ala147Thr TSPO polymorphism in the *TSPO* gene (rs6971). About 10% of humans show low binding affinity to PBR28[24]. A recent study has demonstrated that the rs6971 polymorphism predicts PBR28 binding affinity in human platelets[25]. Since the low-affinity binder phenotype is consistent across all tissues within the same person, testing for the Ala147Thr polymorphism can be performed to predict low affinity for PBR28 in all organs, including the brain[25]. High or Mixed affinity binders (Ala/Ala or Ala/Thr) will be considered eligible, whereas the low affinity binders (Thr/Thr) will be considered ineligible for the study.

Upper Motor Neuron Burden (UMN-B): The UMN-B at screening will be calculated by assessing five bilateral deep tendon reflexes on a scale of 0-4, as well as three pathological reflexes (bilateral Hoffman and Babinski signs, and jaw jerk) 0 or 1, for a total possible score of 45. Subjects screening for the imaging group with scores of 25 or more may be considered eligible.

5.2.2 Subject Exclusion Criteria

Study subjects meeting any of the following criteria during screening evaluations will be excluded from entry into the study:

1- Abnormal liver function defined as AST and/or ALT > 3 times the upper limit of the normal.
2- Renal insufficiency as defined by a serum creatinine > 1.5 times the upper limit of normal.
3- The presence of unstable psychiatric disease, cognitive impairment, or dementia that would impair ability of the participant to provide informed consent, according to PI judgment.
4- Clinically significant unstable medical condition (other than ALS) that would pose a risk to the participant if they were to participate in the study.
5- History of HIV, clinically significant chronic hepatitis, or other active infection.
6- Active participation in another ALS clinical trial within 30 days of the Screening Visit

Study subjects in the Imaging group meeting any of the additional following criteria during screening evaluations will be excluded from entry into the study:

1- Exposure to immunomodulatory medications within 30 days of the Screening Visit.
2- Any contraindication to undergo MRI studies such as
    a. History of a cardiac pacemaker or pacemaker wires
    b. Metallic particles in the body
    c. Vascular clips in the head
    d. Prosthetic heart valves
    e. Claustrophobia
3- Radiation exposure that exceeds the site's current guidelines

4- Current use of tobacco products including cigarettes, cigars, snuff and chewing tobacco, or nicotine replacement products such as gum or patch.
5- Current use of medications / treatments under investigation in ALS clinical trials or use of "off-label" medications for ALS as determined by the clinical judgment of the principal investigator.

5.3 Withdrawal

A study subject will be discontinued from participation in the study if:

- Any clinical AE, laboratory abnormality, concurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).

Subjects are free to withdraw from participation in the study at any time upon request.

5.3.1 Handling of Withdrawals

A subject may choose to discontinue participation in the study at any time. Subjects who permanently discontinue study drug should complete early study drug termination procedures per protocol. The subject should then return any unused study drug and will be asked to return to the study site for a final safety visit. At that visit, the subject will be asked to have a final telephone call 28 days (+ 5 days) after taking their last dose of study drug.

5.3.2 Termination of Study

This study may be prematurely terminated if, in the opinion of the PIs, there is sufficient reasonable cause.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Enrollment is unsatisfactory.
- Insufficient adherence to protocol requirements.
- Data are not sufficiently complete and/or evaluable.

6 TREATMENTS ADMINISTERED

6.1 Treatments

6.1.1 Study Product Description

[redacted]

6.1.2 Treatments administered

RNS60 will be administered in two ways: by IV infusion one day a week (infusion dose: 375 ml, infused over a 40-minute period) and by inhalation (the remaining 6 days a week, 4 ml/day). The nebulizer system supplied is comprised of the PARI Trek S nebulizer compressor and the LC Sprint reusable nebulizer.

[redacted]

[redacted]

RNS60 will be administered intravenously at weekly study visits (starting on the Baseline visit) at the clinic site by properly trained staff designated by the investigator. Subjects will receive 375 ml RNS60 infused over 40 minutes. Infusion documentation should include recording infusion start and stop times, volume infused, and any interruptions to the infusion.

During the remaining days of the week, treatment with RNS60 will be nebulized at home in the morning. [redacted]

6.2 Receiving, Storage, Dispensing

6.2.1 Receipt of Drug Supply

RNS60 will be provided by Revalesio Corporation (Tacoma, WA). The company will supply both the IV and inhalation preparations. RNS60 will be shipped directly to the MGH Research Pharmacy. The Research Pharmacist will be responsible for keeping records of study drug receipt and inventory.

6.2.2 Storage

The drug supply will be kept refrigerated in the MGH Research Pharmacy with access limited to those directly involved in the study.

6.2.3 Dispensing of Study Drug

[redacted]

[redacted]

[redacted]

6.3 Modification of Study Intervention/Investigational Product for a Subject

Any dosage adjustment, including the reason for and dates of adjustment, will be documented in the CRF for each subject requiring this manipulation. The PIs or licensed physician Sub-Investigator may reduce the dosage of study drug or discontinue the study drug in its entirety for AEs thought to be related to the study drug or for other reason during the trial (the reason for, and dates of suspension or dose reduction must be documented). If the AE is mild or moderate, the dosage may be reduced until the event improves. The PIs may then choose to resume the higher dosage or maintain the subject at a reduced dosage. The option to continue with administration by IV only or inhalation only is allowable.

If the event is serious or life threatening, and deemed to be definitely drug related, the study drug will be discontinued immediately. Study subjects must remain off the study drug permanently. Subjects may not resume study drug. All AEs will be followed to resolution.

6.3.1. Dosage Discontinuation

Reasons for discontinuation of study medication may include an AE, PI recommendation, protocol deviation, loss-to-follow-up, patient request, or patient death.

Study subjects who discontinue study drug prematurely (early termination from study) will be encouraged to return for a Final Safety Visit and participate in a Follow-Up Telephone Call 28 days (+ 5 days) after the last dose of study drug.

6.4 Accountability Procedures

Subjects will be provided with a drug diary at each time point when drug for inhalation is dispensed (baseline, week 7, and week 15 for the core study, and week 23, week 30, and week 38 for the extension phase). Subjects will be instructed to return all drug for inhalation consumed and remaining, as well as a completed diary, at weeks 7, 15, 23, 30, 37, and 47. Reconciliation of drug consumed and drug remaining will be logged on the drug dispensing and return log, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6.5 Assessment of Subject Compliance

Subjects will be instructed to return empty study medication containers at weeks 7, 15, 23, 30, 37, and 47. Site personnel will review returned study medication to determine compliance.

6.6 Prior and Concomitant Therapy

Throughout the study, the subject may be prescribed concomitant medications or treatments deemed necessary to provide adequate supportive care provided that the medications are licensed in the United States. All concomitant medications and/or treatments received by a subject should be recorded on the appropriate source document and eCRF.

6.6.1 Prohibited Medications and Contraindications

<u>Prohibited Medications</u>

Prohibited medications for subjects in the Imaging group are as follows:

1- immunomodulatory medications
2- nicotine replacement products such as gum or patch

Additionally, subjects in the Biomarker group should wash from benzodiazepines and non-steroidal anti-inflammatory medications one week prior to PET scan as these compounds would affect the results of the scan.

Pregnancy & Nursing Mothers

There are no adequate and well-controlled studies in pregnant women. Subjects or partners of male subjects should not become pregnant during the study or 3 months after stopping study drug. If a female subject becomes pregnant, study treatment must be discontinued immediately.

[redacted]

6.7 Statistical considerations

Sample size calculation was based on the primary outcomes of safety and tolerability. With a sample size of 15 participants, we will have over a 90% chance of seeing at least one occurrence of any adverse event whose probability of occurrence is 15% or greater. Tolerability will be defined as the ability of subjects to complete the entire 24-week treatment portion of study. With 15 participants on active drug in this study, if 10 or more participants tolerate the drug, there is an 85% chance that the true tolerability among people with ALS is at least 75%. Furthermore, if 10 or more people tolerate the drug, there is only a 3% chance that the true tolerability will be as low as 40% in people with ALS. For people in the Biomarker group, primary outcomes will include changes in the ROI in the motor cortex as assessed by [11C]-PBR29-PET. Our previous studies comparing mean PBR28 binding in the motor cortices in limb-onset ALS subjects (1.18 units) with matching healthy volunteers (1.064 units) revealed 0.116 mean difference between the two groups, with 0.08 standard deviation in the ALS group. With 10 people in the Biomarker group, the probability is 90 percent that the study will detect a treatment difference at a one-sided 0.1 significance level if the true difference is 0.096 units.

7 STUDY SCHEDULE

No study procedures should be performed prior to the signing of the informed consent form (ICF). All subjects will sign an ICF prior to undergoing any study tests or procedures. Visit windows (±3 days) are consecutive calendar days and the target visit dates are calculated from the Baseline Visit.

7.1 Screening Visit

The following procedures will be performed at an office visit to determine the subject's eligibility for the study:

- Obtain written informed consent from subject
- Assess inclusion and exclusion criteria
- Obtain medical history and demographics
- Obtain ALS diagnosis history
- Perform physical examination
- Perform neurological examination (including UMN-B for the Imaging group)
- Measure vital signs including height and weight
- Collect blood and urine for safety labs
- Collect blood for TSPO testing (Imaging group ONLY)
- Perform ECG
- Review and document concomitant medications and therapies
- Assess and document AEs

If time permits, ATLIS (strength testing) will be performed for all participants at the screening visit. This may facilitate a more accurate baseline assessment as some individuals may benefit from a learning effect.

7.1.1 Screen Failures

Any subject who signs consent will be considered enrolled in the study. If a subject fails screening, *at a minimum*, the following information should be captured and entered in the Electronic Data Capture (EDC) System:

- Demographics
- Inclusion and Exclusion criteria
- Reason for screen failure
- Screening labs results

7.2 Baseline Visit

This visit will take place within 6 weeks of the Screening Visit. The following procedures will be performed:

- Review inclusion and exclusion criteria
- Measure vital signs including weight
- Collect blood and urine for safety labs
- Perform ECG
- Collect blood samples for biomarkers
- Administer ALSFRS-R questionnaire
- Perform U. Penn upper motor Neuron Burden (UMNB)
- Perform Pulmonary Function Tests
- Measure baseline strength (ATLIS)
- Columbia Suicide Severity Rating Scale (C-SSRS) – Baseline
- Administer 1st dose of study drug.
- Dispense study medication (for inhalation use) for the following 8 weeks
- Review and document concomitant medications and therapies
- Assess and document AEs

Pre- treatment neuroimaging study (MRI/PET) (Imaging group only) will take place after TSPO affinity test results are available. This may occur on any day between release of TSPO test results and Baseline, or on the same day as the Baseline Visit. This first neuroimaging study will be performed before any treatment is administered. ALSFRS-R and SVC will be repeated on the same day as the scan. STAT quantitative serum human chorionic gonadotropin (hCG) testing will also be performed prior to the MRI/PET scan for all women of childbearing potential (WOCBP).

7.3 Weekly study visits (Week 1 through Week 10, Week 12 through Week 22, Week 24 through 34, and Week 36 through 46)

Subjects will return to MGH on a weekly basis until Week 22. The following procedures will be performed at the Week 1 through Week 10, Week 12 through Week 22, Week 24 through 34, and Week 36 though 46 visits:

- Vital signs including weight
- Administer study drug via IV infusion
- Review and document concomitant medications and therapies
- Assess and document AEs
- Check study drug compliance and accountability
- Dispense study medication (for inhalation use) (at Week 7, Week 15, Week 23, Week 30 and Week 38 only)

Post-treatment neuroimaging study (MRI/PET) (Imaging group only) will be performed at one time only between the Week 18 and Week 23 visits. ALSFRS-R and SVC will be repeated on the

same day as the scan. STAT quantitative serum hCG testing will also be performed prior to the MRI/PET scan for all WOCBP.

Subjects who wish to continue to take study drug as part of the optional extension phase will sign consent between Weeks 18 and 23.

7.4 Week 11 Visit

The following procedures will be performed at the Week 11 visit:

- Measure vital signs including weight
- Collect blood and urine for safety labs
- Collect blood for biomarkers
- Administer ALSFRS-R questionnaire
- Perform U. Penn upper motor Neuron Burden (UMNB)
- Perform Pulmonary Function Tests
- Measure strength (ATLIS)
- Columbia Suicide Severity Rating Scale (C-SSRS) – Since last visit
- Administer study drug via IV infusion
- Check study drug compliance and accountability
- Review and document concomitant medications and therapies
- Assess and document AEs

7.5 Week 23 Visit

The following procedures will be performed at the Week 23 visit:

- Measure vital signs including weight
- Perform ECG
- Perform neurological exam
- Perform physical exam
- Collect blood and urine for safety labs
- Collect blood for biomarkers
- Administer ALSFRS-R questionnaire
- Perform U. Penn upper motor Neuron Burden (UMNB)
- Perform Pulmonary Function Tests
- Measure strength (ATLIS)
- Columbia Suicide Severity Rating Scale (C-SSRS) – Since last visit
- Administer study drug via IV infusion
- Review and document concomitant medications and therapies
- Assess and document AEs
- Check study drug compliance
- For those subjects that do not wish to continue, perform study drug accountability and collect all unused study drug, empty containers and nebulizers
- For those subjects that wish to participate in the 24-week extension phase, medication for inhalation will be dispensed at this visit

7.6 Week 35 Visit

The following procedures will be performed at the Week 35 visit:

- Measure vital signs including weight
- Perform ECG
- Collect blood and urine for safety labs
- Administer ALSFRS-R questionnaire
- Perform Pulmonary Function Tests
- Columbia Suicide Severity Rating Scale (C-SSRS) – Since last visit
- Review and document concomitant medications and therapies
- Assess and document AEs
- Check study drug compliance and accountability

7.7 Week 47 Visit

The following procedures will be performed at the Week 23 visit:

- Measure vital signs including weight
- Perform ECG
- Perform neurological exam
- Perform physical exam
- Collect blood and urine for safety labs
- Administer ALSFRS-R questionnaire
- Perform Pulmonary Function Tests
- Columbia Suicide Severity Rating Scale (C-SSRS) – Since last visit
- Review and document concomitant medications and therapies
- Assess and document AEs
- Check study drug compliance
- Perform study drug accountability and collect all unused study drug, empty containers and nebulizers

7.8 Week 28 or 52 Phone Interview

The following procedures will be performed at the Week 28 Phone Call:

- Administer ALSFRS-R questionnaire
- Review and document concomitant medications and therapies
- Assess and document AEs

7.9 Final Safety Visit

Subjects who withdraw consent will be asked to come in for a Final Safety Visit as soon as possible, and will be asked to have a final Follow-Up Telephone Call (+ 5 days, but no earlier than 28 days, after subject's last dose of study drug) to assess for adverse events.

The following will be performed at the Final Safety Visit:

- Measure vital signs
- Perform ECG
- Perform neurological exam
- Perform physical exam
- Collect blood samples for safety labs
- Collect blood for biomarkers
- Administer ALSFRS-R questionnaire
- Perform U. Penn upper motor Neuron Burden (UMNB)
- Perform Pulmonary Function Tests
- Measure strength (ATLIS)
- Columbia Suicide Severity Rating Scale (C-SSRS) – Since last visit
- Review and document concomitant medications and therapies
- Assess and document AEs
- Check study drug compliance
- Perform study drug accountability and collect all unused study drug and empty containers and nebulizers

7.10 Follow-up

After the Week 28 Follow-up Telephone Interview, subjects may be contacted every three months for up to two years, or until consent is withdrawn, in order to obtain vital status and clinical information including the ALSFRS-R. Additionally, two years of post-study access to subjects' medical records will be requested to allow for review in combination with study data in order to investigate any correlation between imaging data collected during this study and subjects' clinical outcomes.

8 CLINICAL ASSESSMENTS AND OUTCOME MEASURES

8.1 Clinical Variables

Assessments will be performed at designated time-points throughout the study for clinical evaluation. In addition to the assessments evaluated below, subjects will provide information on their demographics, past medical history, including ALS, as well as concomitant medication usage.

8.1.1 Vital Signs, Height & Weight

Vital signs, including systolic and diastolic blood pressure, pulse rate (radial artery)/minute, respiratory rate/minute, temperature and weight will be assessed at specified visits. Height will be measured and recorded at the Screening Visit only.

8.1.2 Clinical Laboratory Assessments

The following safety laboratory tests will be performed during the study:

- Hematology with differential panel and urinalysis: complete blood count with differential (hematocrit, hemoglobin, platelet count, RBC indices, Total RBC, Total WBC, and WBC & differential)
- Blood chemistry panel/Liver function tests (LFTs): alanine aminotransferase (ALT (SGPT)), aspartate aminotransferase (AST (SGOT)), albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, magnesium, phosphate, potassium, sodium, total bilirubin and total protein
- Urine human chorionic gonadotrophin (hCG) for women of childbearing potential (WOCBP) STAT quantitative serum hCG testing will also be performed prior to the MRI/PET scan for all WOCBP.

Additional testing may be ordered if needed, to further assess an AE, or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

8.1.3 Physical Examination

A physical examination will be performed and recorded. The following systems will be examined: head/neck, eyes, ears, nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, central nervous system, extremities, and skin.

8.1.4 Neurological Examination

A neurological examination will be performed and recorded.

8.1.5 Adverse Events

AEs will be documented at each study visit, including the final telephone call 28 days after the last dose of study drug. Information on adverse effects of study medication and on inter-current events will be determined at each visit by direct questioning of the subjects and review of concomitant medications.

8.1.6 ALSFRS-R

The ALSFRS-R is a quickly administered (5 minutes) ordinal rating scale (ratings 0 to 4) used to determine subjects' assessment of their capability and independence in 12 functional activities. All 12 activities are relevant in ALS. Initial validity was established by documenting that in ALS patients, change in ALSFRS-R scores correlated with change in strength over time, was closely associated with quality of life measures, and predicted survival. The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that the categories are relevant to ALS, it is a sensitive and reliable tool for assessing activities of daily living function in those with ALS, and it is quickly administered. With appropriate training the ALSFRS-R can be administered with high inter-rater reliability and test-retest reliability. The ALSFRS-R can be administered by phone with good inter-rater and test-retest reliability. The equivalency of phone versus in-person testing, and the equivalency of study subject versus caregiver responses have also recently been established. Therefore, if necessary, the ALSFRS-R may be given to the study subject over the phone.

8.1.7 Pulmonary Function Testing

Pulmonary Function Testing includes Slow Vital Capacity (SVC).

Slow Vital Capacity (SVC): The vital capacity (VC) (percent of predicted normal) will be determined, using the upright slow VC method. The VC can be measured using conventional spirometers that have had a calibration check prior to subject testing. A printout from the spirometer of all VC trials will be retained. Three VC trials are required for each testing session, however up to 5 trials may be performed if the variability between the highest and second highest VC is 10% or greater for the first 3 trials. Only the 3 best trials are recorded on the CRF.

8.1.8 C-SSRS

The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA)[62]. The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical

trials of antidepressant drugs. One such assessment instrument is the Columbia Suicide Severity Rating Scale (C-SSRS)[63]. The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

Only investigators who have been fully trained in the administration of the C-SSRS will assess subject suicidality. As part of training, investigators are prepared to respond to and manage instances in which patients express suicidal ideation or exhibit suicidal behavior.

At the Baseline Visit, the C-SSRS *Baseline* version will be administered. This version is used to assess suicidality over the subject's lifetime and specifically for the previous 6 month time period.

At the Week 11, Week 23, Week 35, Week 47, and the Final Safety visit, as applicable, the *Since Last Visit* version of the C-SSRS will be administered. This version of the scale assesses suicidality since the subject's last visit.

Information obtained from: *http://www.cssrs.columbia.edu/*

8.1.9 Upper Motor Neuron-Burden (UMN-B)

The Penn Upper Motor Neuron-Burden (UMN-B) is the total number of pathological UMN signs on examination including pathologically brisk biceps, supinator, triceps, finger, knee and ankle reflexes, and extensor plantar responses assessed bilaterally and brisk facial and jaw jerks (9). The scale is a combination of Ashworth, Reflexes, and Pseudobulbar Affect scale (Range score: 0 to 32).

The UMN also includes scoring of the Center for Neurologic Study-Lability Scale (CNS-LS), a 7-item self report scale that assesses pseudobulbar affect (PBA) by measuring the perceived frequency of PBA episodes (laughing or crying) and the Ashworth Spasticity Scale, a standard measure for spasticity that has been used in numerous ALS clinical trials to assess spasticity due to upper motor neuron dysfunction in ALS. Data is generated from the clinical exam and scored from 1 to 5, the lowest score indicating normal tone and the highest extreme spasticity.

8.1.10 Blood Biomarkers

Subjects will also be asked to provide blood samples for biomarker analysis per Schedule of Activities. These blood samples will be stored in a sample repository. These samples will be used for biomarker research. All samples will be labeled with a code. The code will not include any identifiable information. Any analysis performed on these samples is for research purposes only.

Unused samples will remain in the biorepository for future ALS-related research. There is no scheduled date on which the samples will be destroyed. Samples may be stored for research until they are used, damaged, decayed or otherwise unfit for analysis. Subjects have the option of declining participation in this portion of the study at any time by withdrawing their consent to have their sample used. However, it will not be possible to destroy samples that may have already been used.

8.1.11 Strength measurement (ATLIS)

Changes in strength will be measured using ATLIS (Accurate Test of Limb Isometric Strength), a non-invasive device that allows measurements of isometric strength in 12 muscle groups of the arms and legs using a standard protocol (elbow and knee flexion and extension, grip, and dorsiflexion). ATLIS consists of a frame with metal uprights. A wireless load cell is attached to adjustable testing stations positioned on the frame. The load cell transmits data (peak force) to a laptop computer using wireless technology. The General Hospital Corporation was granted a patent for this device by the US Patent Office (Patent # 7,493,812 issued 2/24/09). This device is not FDA approved.

8.1.12 Neuroimaging

Subjects in the Imaging group will undergo Magnetic Resonance Imaging (MRI) / Positron Emission Tomography (PET) twice during the course of the study. MR-PET scanning will be performed simultaneously using the Siemens 3 Tesla TIM Trio whole-body MRI system with a head PET camera insert. The goal of these scans is to measure activated microglia in study participants before treatment and after several weeks of treatment. The first scan will occur between the Screening and the Baseline visits (*off* treatment), after subject eligibility has been confirmed by TSPO affinity binding assay. The second scan will occur between the Week 18 and Week 23 visits (*on* treatment). Neuroimaging will be performed at the MGH Martinos Center for Biomedical Imaging. Subjects will be asked to lie still in a supine position for the duration of the study, which will take approximately 90 min.

9 SAFETY AND ADVERSE EVENTS

The AE definitions and reporting procedures provided in this protocol comply with all applicable regulations and ICH guidelines. The PIs will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. It is also important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

9.1 Definitions of AEs, Suspected Adverse Drug Reactions & SAEs

9.1.1 Adverse Event and Suspected Adverse Drug Reactions

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of AEs include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as AEs in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered AEs. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as AEs.

AEs are generally detected in two ways:

Clinical → symptoms reported by the subject or signs detected on examination.

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures, the results of which are not being captured as AEs).

For the purposes of this study, symptoms of progression/worsening of ALS, including 'normal' progression, will be recorded as AEs.

The following measures of disease progression will not be recorded as AEs even if they worsen (they are being recorded and analyzed separately): vital capacity results and ALSFRS-R results.

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the PI and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the PI.

Subjects will be monitored for AEs from the time they sign consent until completion of their participation in the study (defined as death, consent withdrawal, loss to follow up, early study termination for other reasons or following completion of the entire study).

9.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the PI or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).

6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical AE may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

The PI is responsible for classifying AEs as serious or non-serious.

9.2 Assessment and Recording of Adverse Events

The PIs will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. All AEs will be collected and reported in the electronic data capture (EDC) system. The PIs shall promptly review all information relevant to the safety of the investigational product, including all SAEs. Special attention will be paid to those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

9.2.1 Assessment of Adverse Events

At each visit (including telephone interviews), the subject will be asked if they have had any problems or symptoms since their last visit in order to determine the occurrence of AEs. If the subject reports an AE, the Investigator will probe further to determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

9.2.2 Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the PIs, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.

2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.

3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (Suspected ADR)

4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (Suspected ADR)

5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (Suspected ADR)

9.2.3 Recording of Adverse Events

All clinical adverse events are recorded in the Adverse Event (AE) Log in the subject's study binder. Study staff should fill out the AE Log and enter the AE information into the EDC system within 48 hours of the site learning of a new AE or receiving an update on an existing AE.

Entries on the AE Log (and into the EDC) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

10 SAFETY MONITORING

10.1 Safety Monitoring

The study PIs will review safety data throughout the trial and may stop the trial for safety if they determine that there is a significant difference in the rate of a particular adverse event that would indicate a risk that is greater than the possible benefit of the study drug.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the Partners Human Research Committee (PHRC) in accordance with PHRC unanticipated problems including AEs reporting guidelines.

11 DATA COLLECTION

All data collected as part of this study will be entered into an EDC maintained by the Massachusetts General Hospital (MGH) Neurological Clinical Research Institute (NCRI). This platform facilitates:

1. Capture of clinical and research data from neurologic patients for individual projects in a structured and secure system;
2. Aggregating and sharing uniform, deidentified and/or anonymized datasets for secondary analyses.

11.1 ROLE OF DATA MANAGEMENT

Data Management (DM) is responsible for the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with applicable Sponsor and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, Case Report Forms (CRFs), and/or other forms used to report, track and record clinical research data. DM is responsible for developing, testing, and managing clinical data management activities.

11.1.1 Data Entry and Checks

The site personnel are instructed to enter information into the EDC. Data capture is the responsibility of the staff at the site under the supervision of the PIs. During the study, the PIs must maintain complete and accurate documentation for the study. The EDC provide password protection. An edit checking and data clarification process will be put in place to ensure accuracy of the data. Logic and range checks as well as more sophisticated rules may be built into the eCRFs to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data that are out of range, out of window, missing or not calculated correctly.

11.1.2 Data Lock Process

The platform will have the ability to lock the project-specific visits to prevent any modification of data once the project is closed. Once this option is activated, every user will have Read-Only access to the data.

11.1.3 Data handling and record keeping

The PIs are responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained.

11.2 CONFIDENTIALITY

The EDC software and patient data reside on servers located in the Partners Healthcare Systems (Partners) server farm. Physical and software access to the servers and security is provided by the Partners IT department.

11.3 RETENTION OF RECORDS

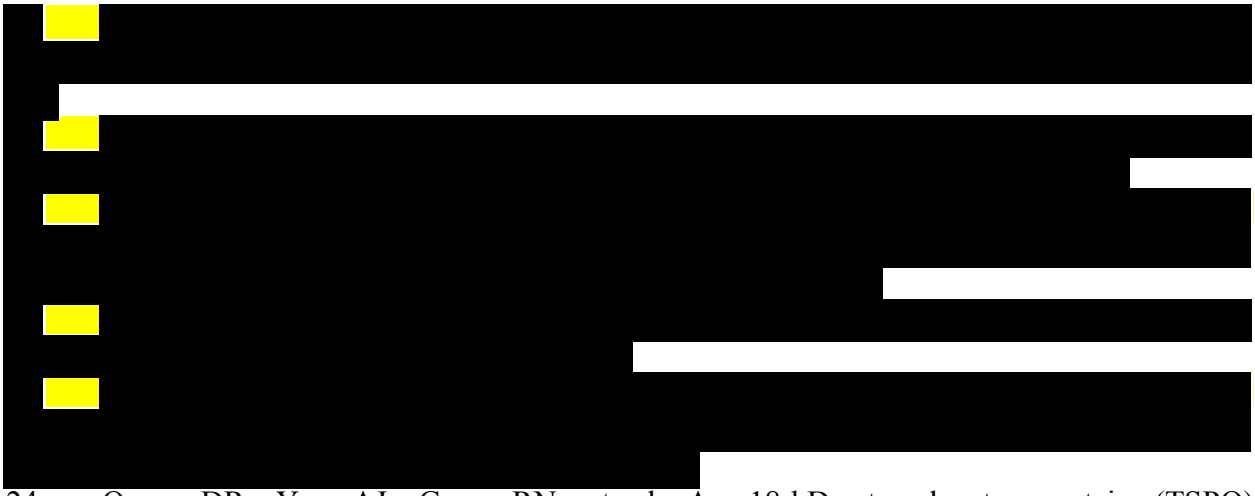
Research records will be retained in accordance with site IRB policies.

11.4 PUBLICATIONS

The PIs will be responsible for publications of results from this trial. Responsibilities will include the following:

- Analyze and interpret data gathered in this study, and write publications from these data.
- Submit manuscripts to selected journals and address peer reviewers' comments.
- Submit abstracts to selected meetings and present data at the meetings.
- Determine authorship on the basis of the Uniform Requirements for Manuscripts.

12 LITERATURE REFERENCES



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13 APPENDICES

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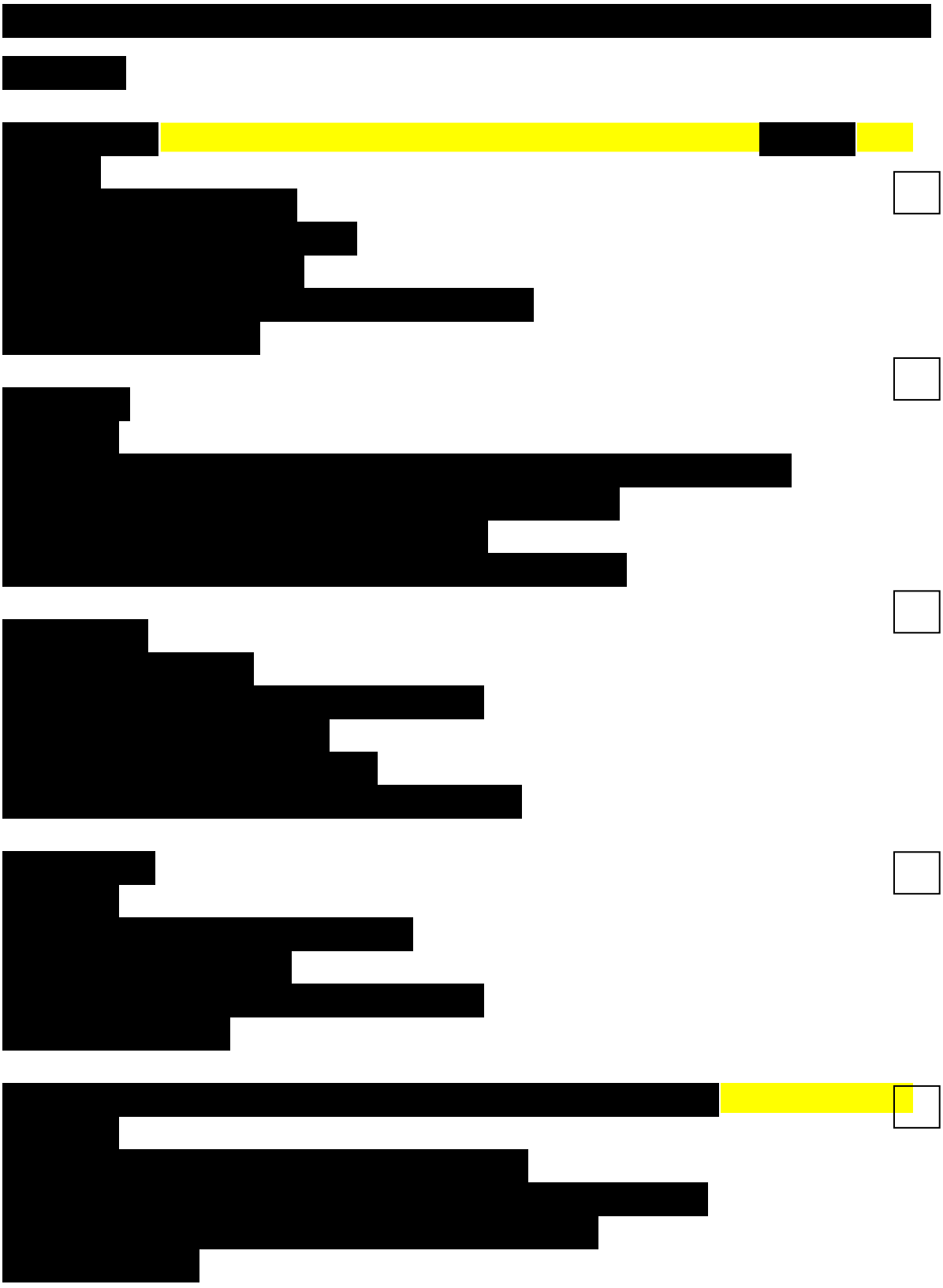

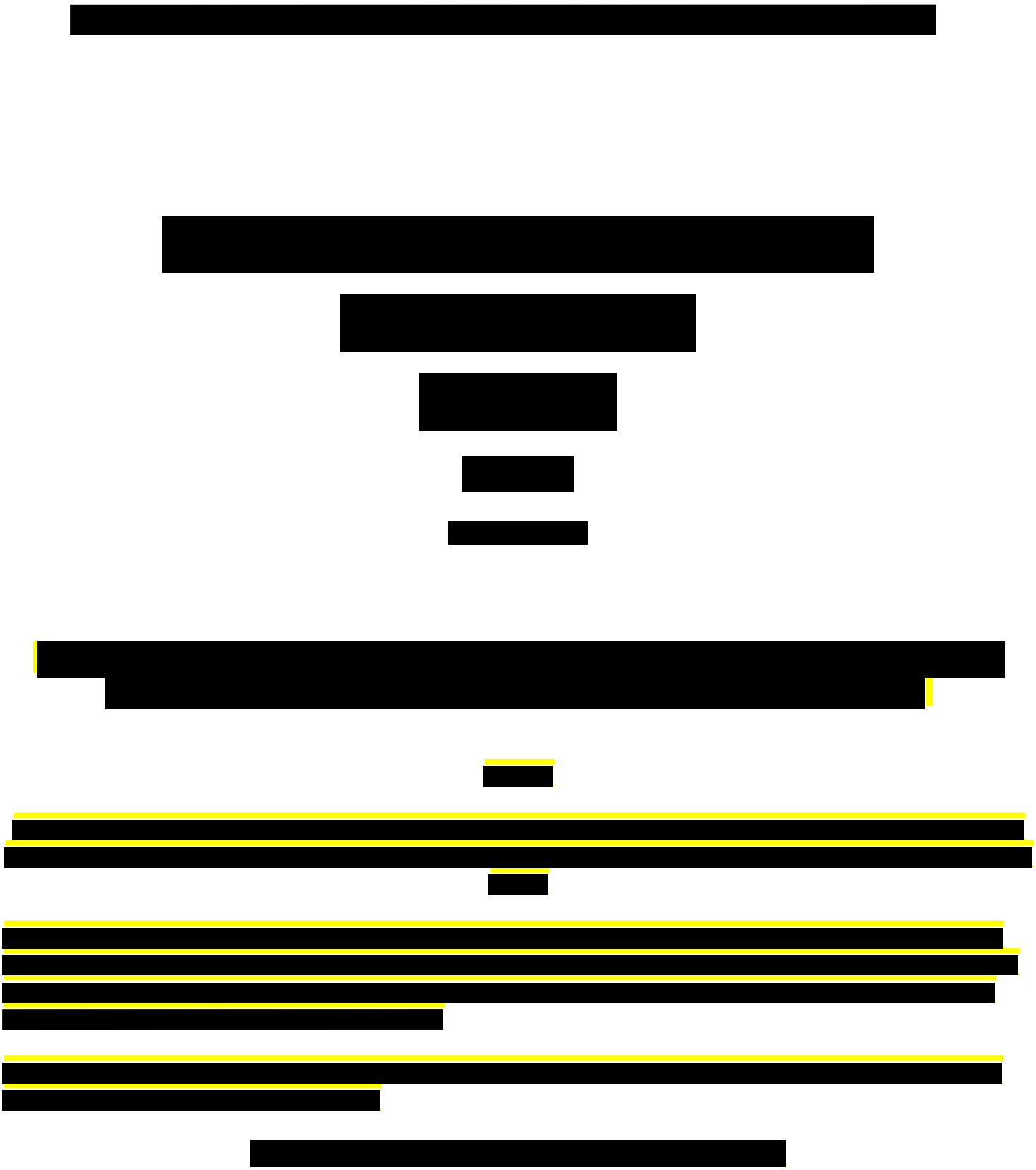

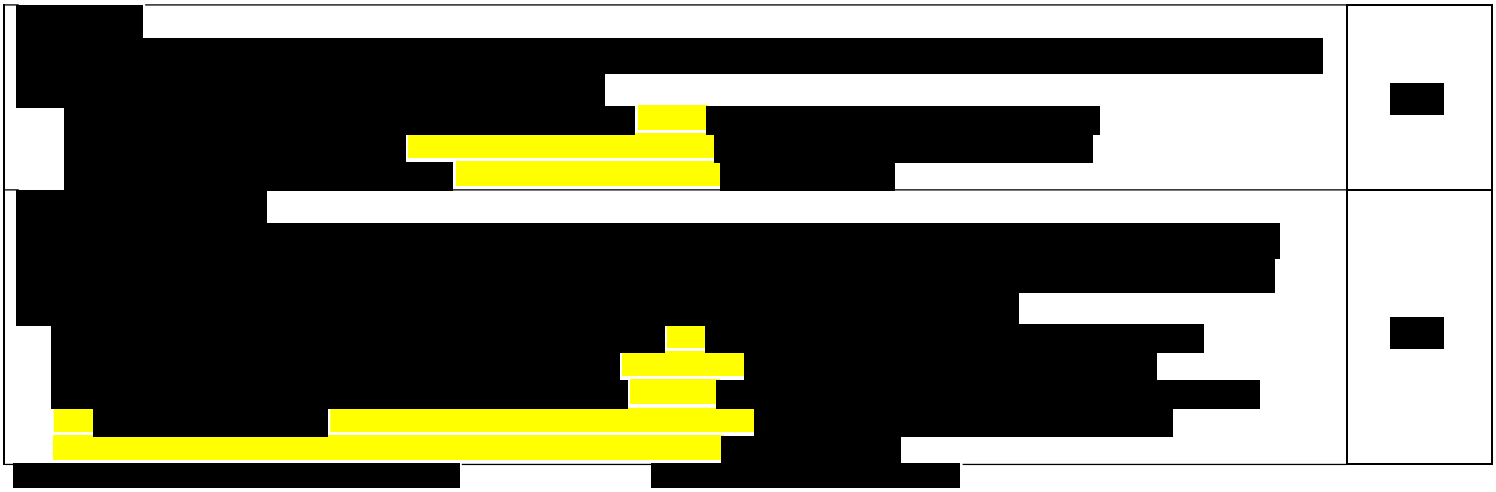

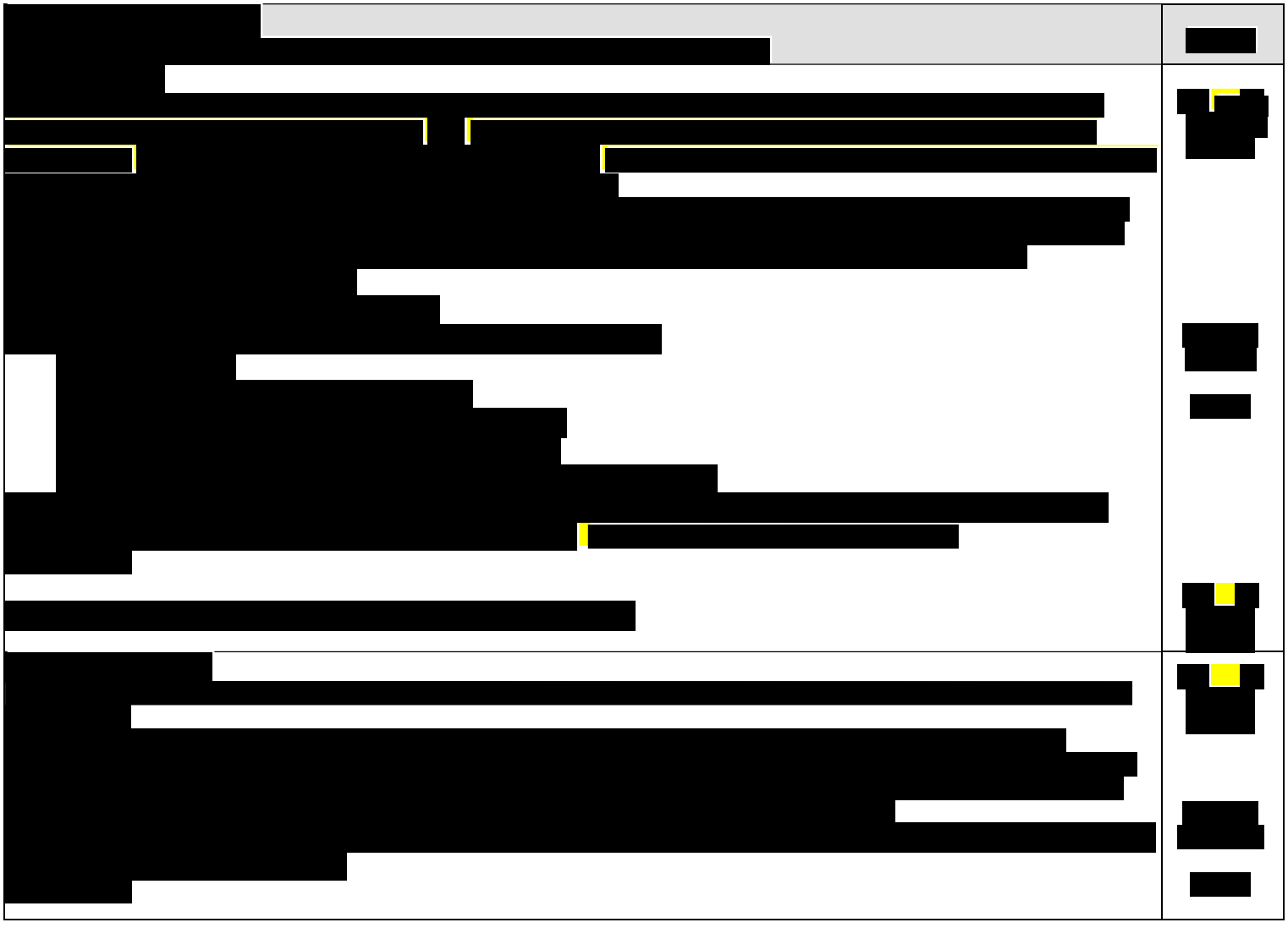

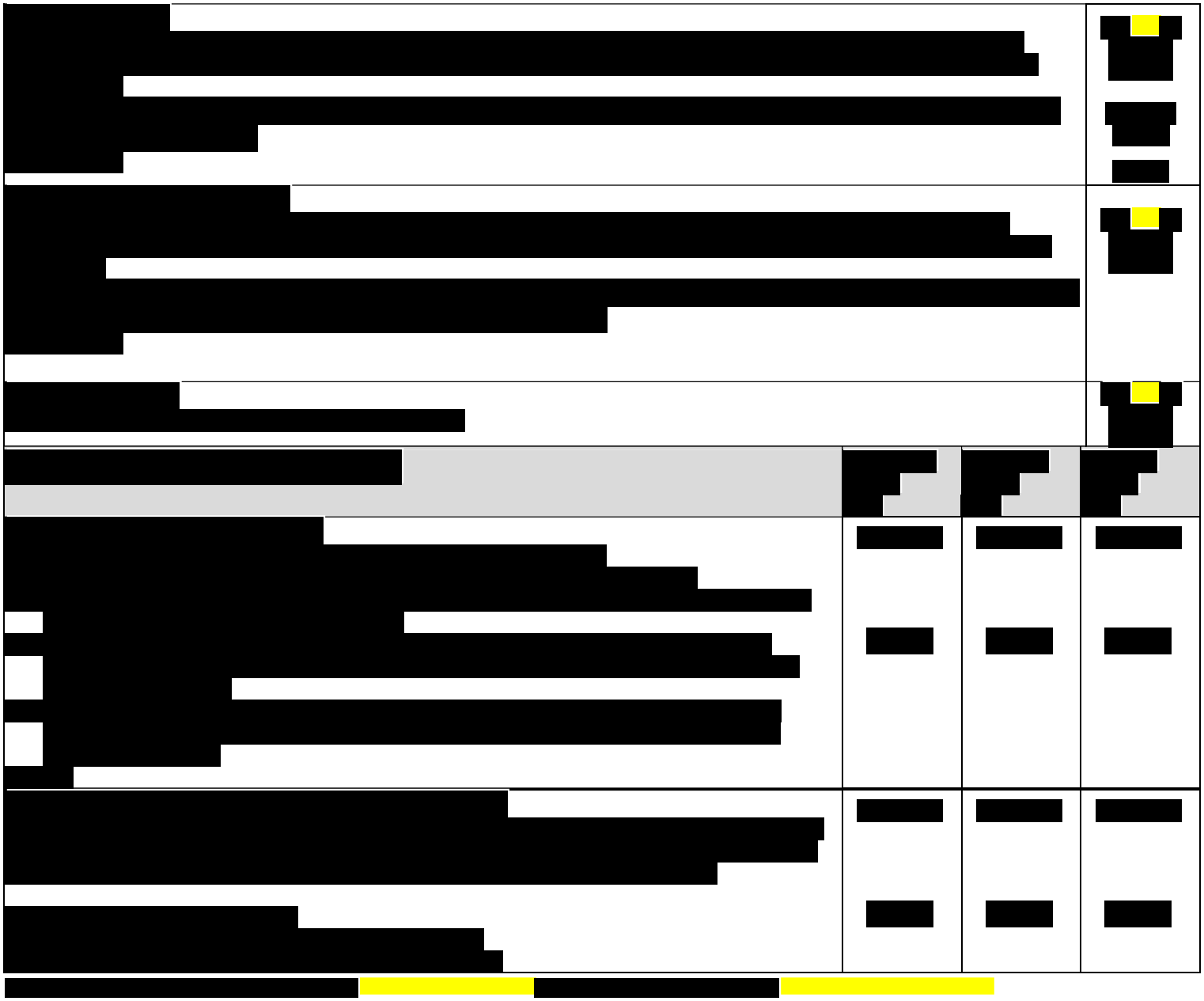

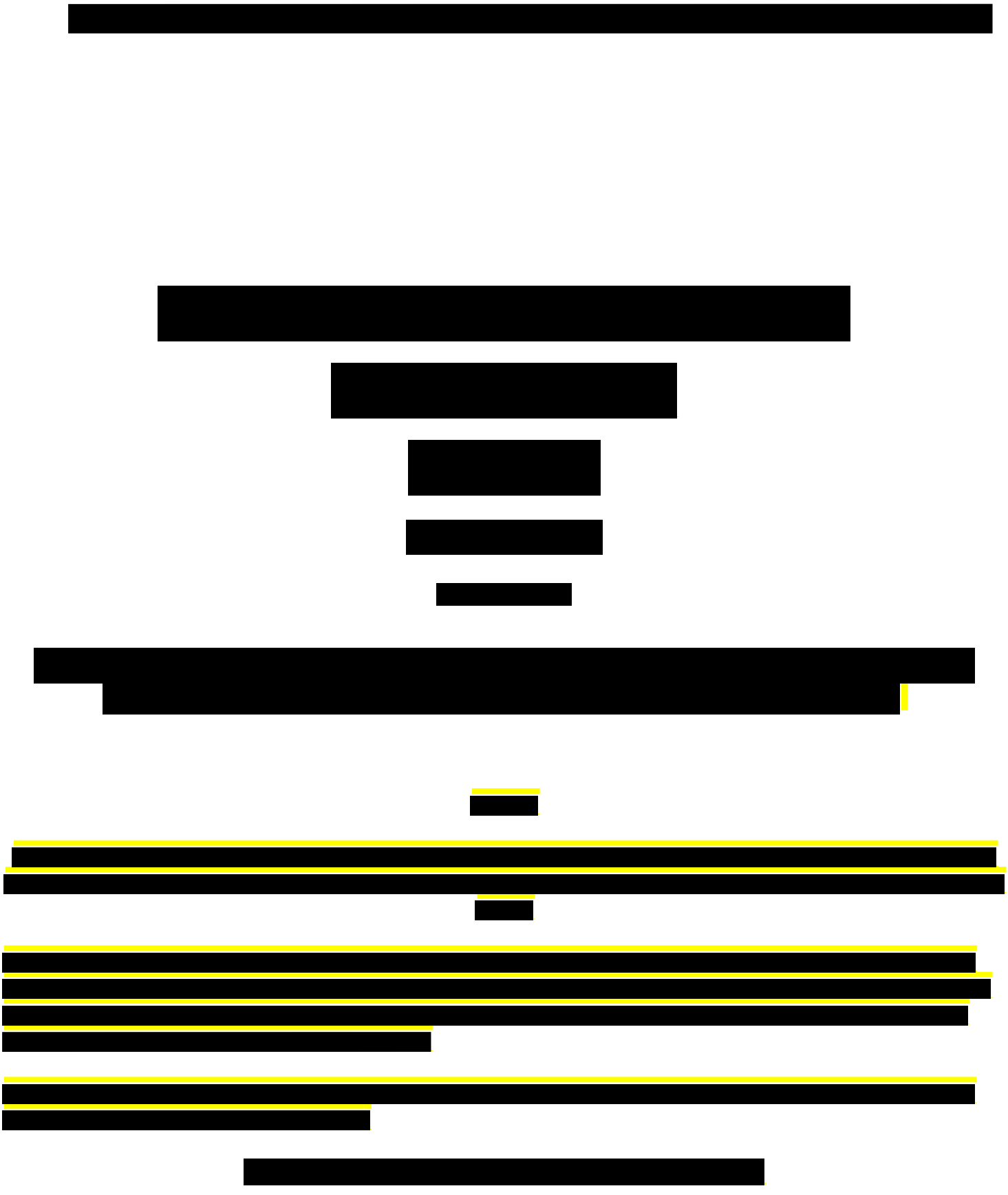

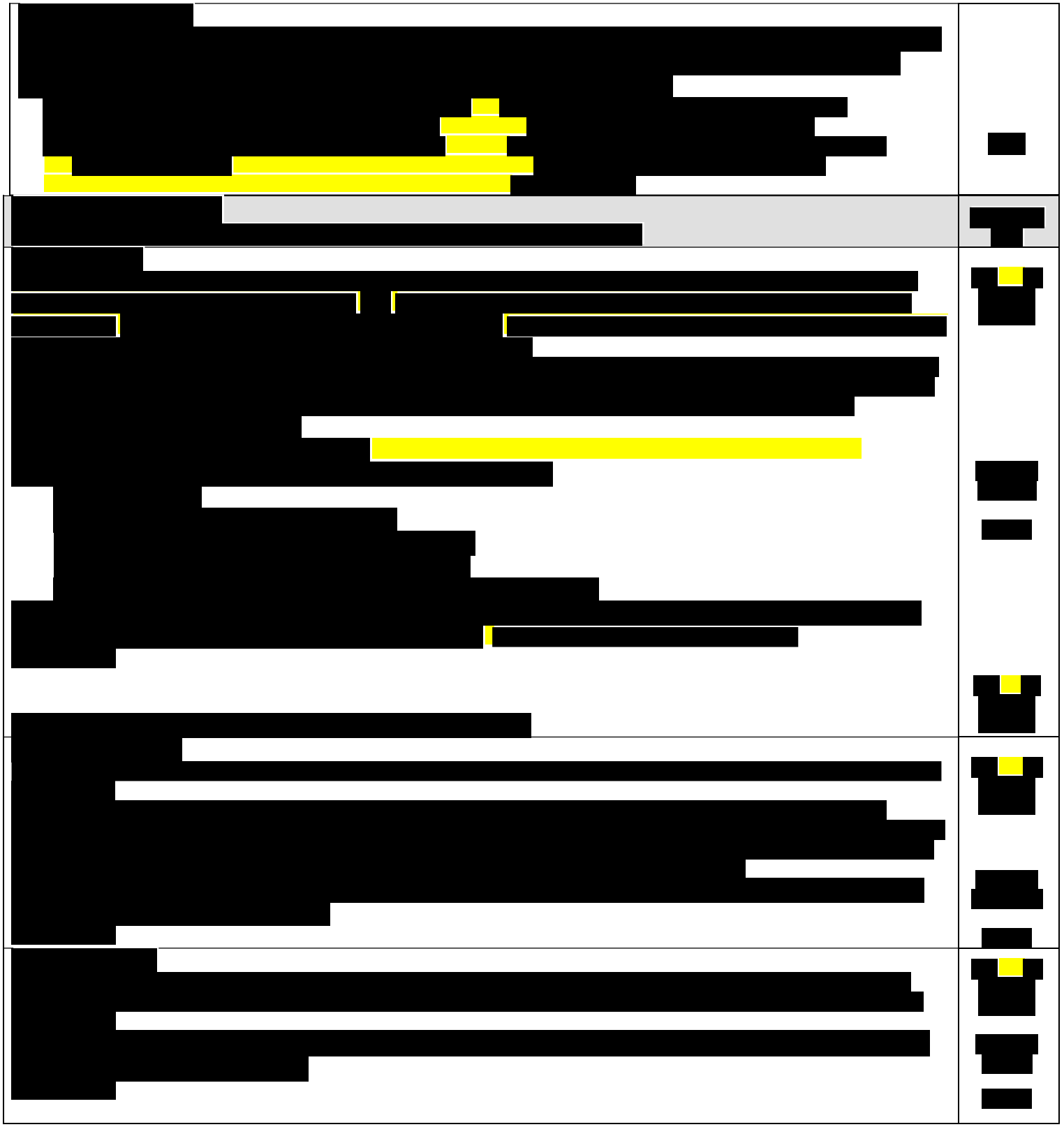

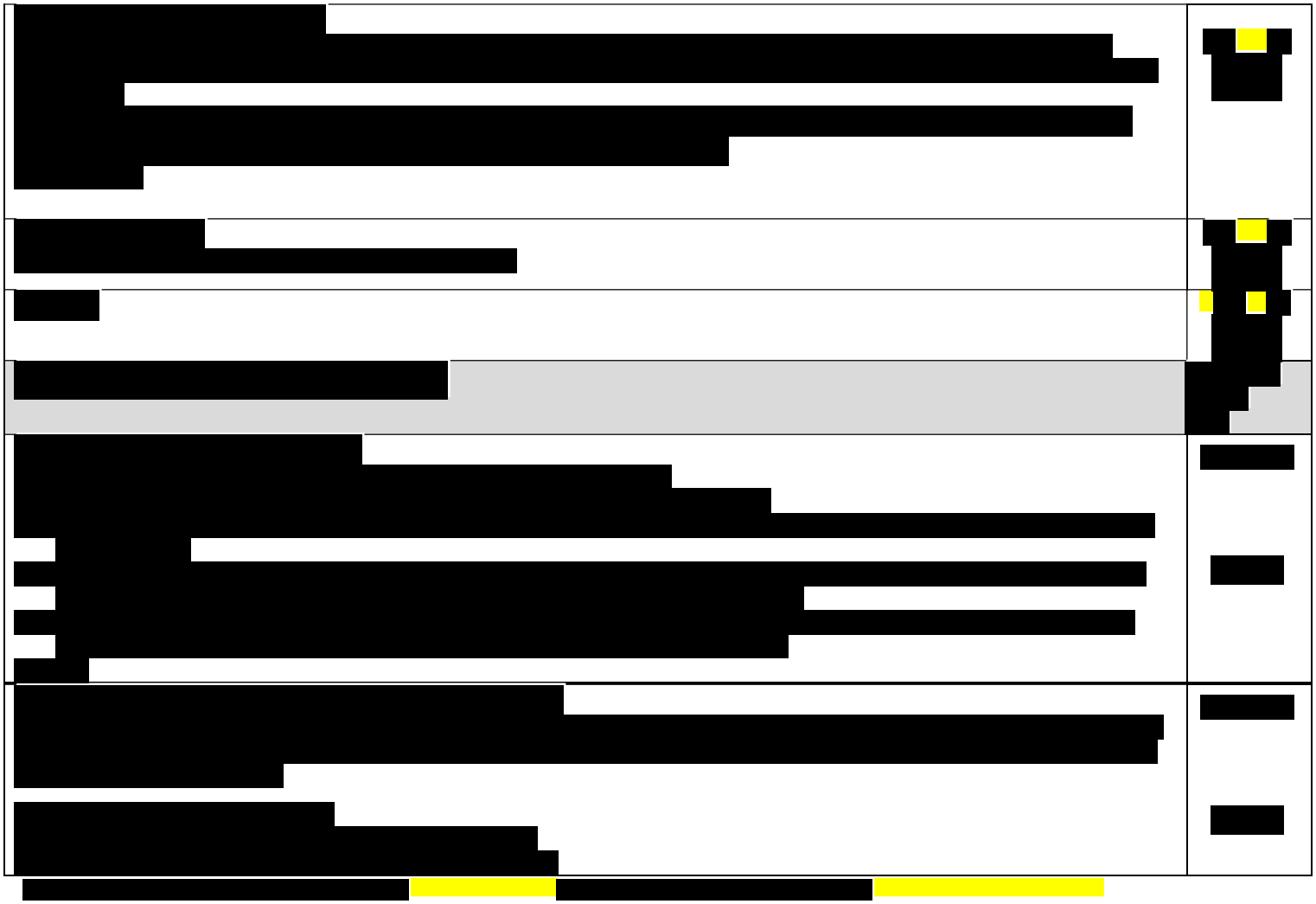

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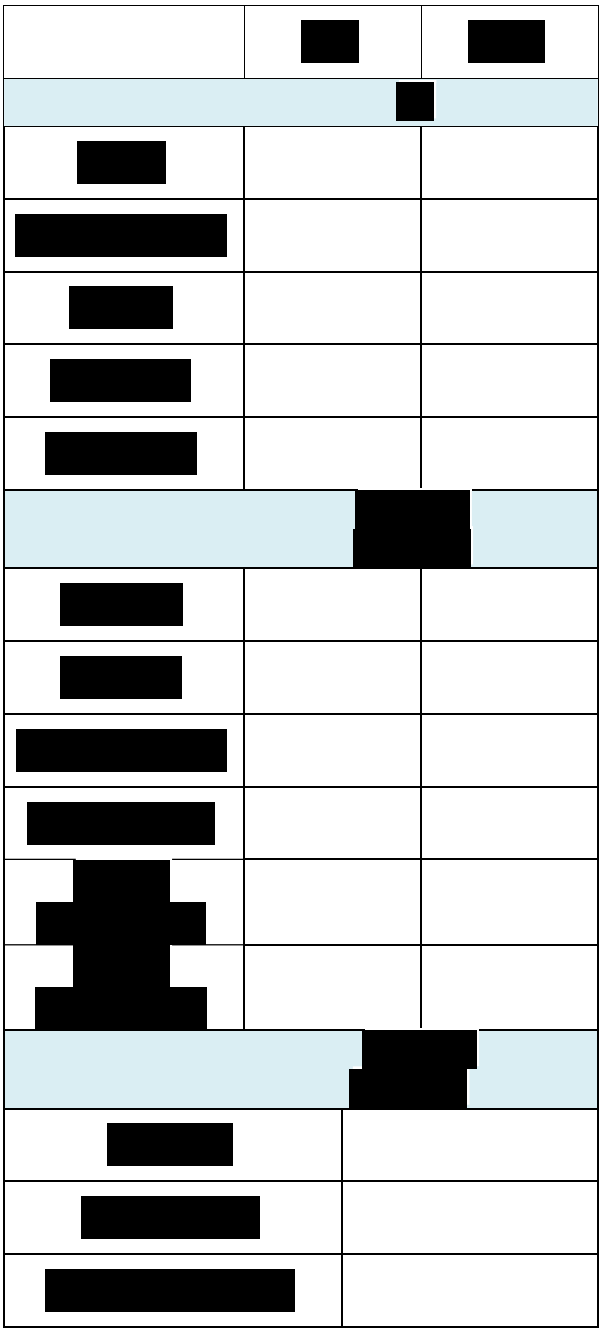

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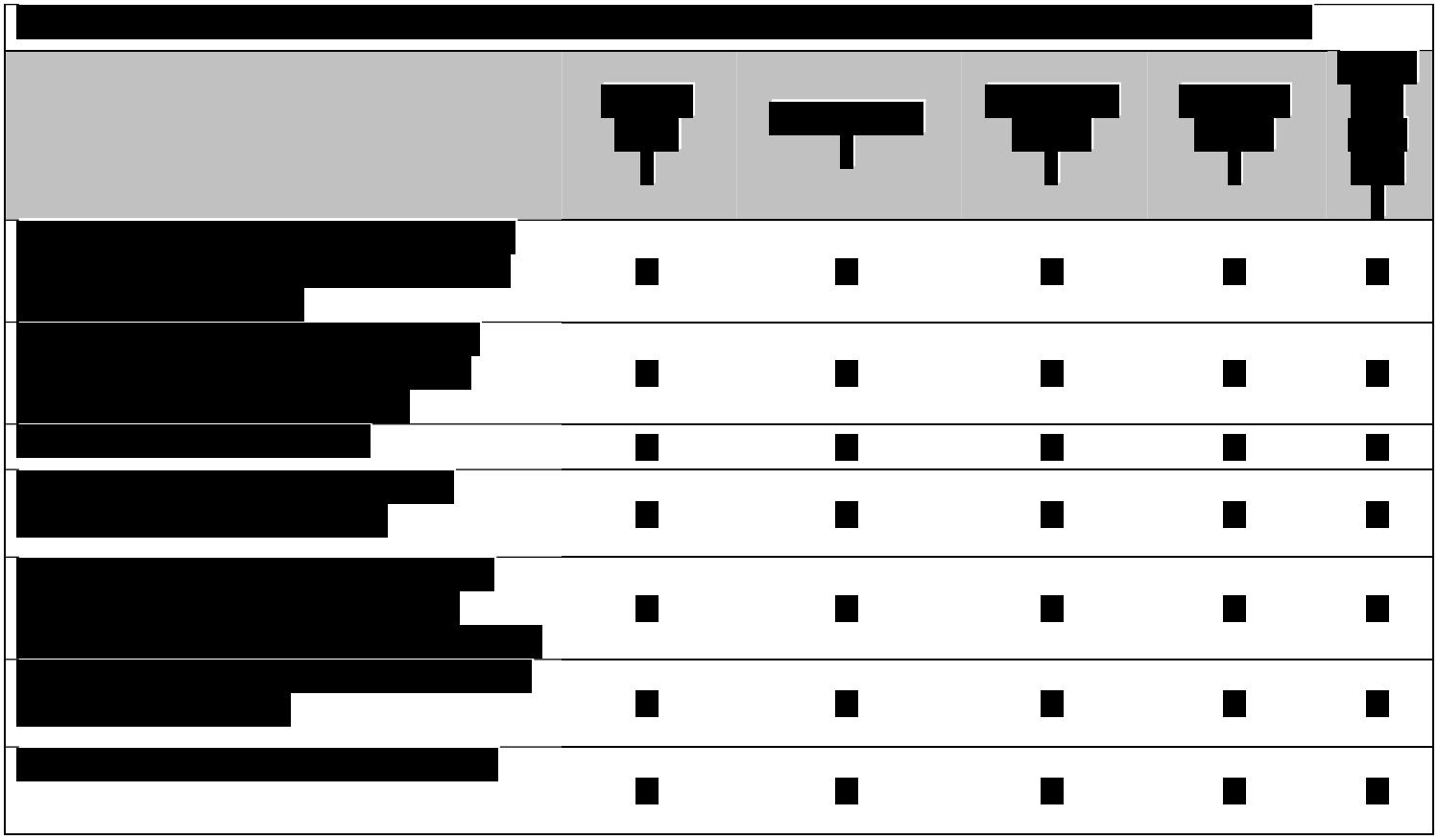

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