Statistical Analysis Plan

A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache

Study Number TV48125-CNS-30058

NCT03107052

SAP Approval Date: 15 July 2019

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Phase 3

IND number: 129606; **EudraCT number: 2016-003172-43**

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Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **TV48125-CNS-30058**

Study Title: **A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache**

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Safety**

Amendment: N/A

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	antidrug antibodies
β-HCG	beta-human chorionic gonadotropin
CCH	chronic cluster headache
CH	cluster headache
CNS	central nervous system
CRF	case report form
CV	coefficient of variation
e-diary	electronic diary
ECG	electrocardiogram/electrocardiography
ECH	episodic cluster headache
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
EOT	end of treatment
EQ-5D	EuroQol-5 Dimension
[redacted]	[redacted]
GCRP	genetic polymorphisms within the calcitonin gene-related peptide
HADS	Hospital Anxiety and Depression Scale
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous(ly)
MCS	Mental Health Composite Scores
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	non-steroidal anti-inflammatory drug
PCS	Physical Composite Scores
PGIC	Global Impression of Change
PPSI	Patient-Perceived Satisfactory Improvement
R&D	Research and Development
SAP	statistical analysis plan
sc	subcutaneous(ly)
SD	standard deviation
SE	standard error
SF-12	12-Item Short-Form Health Survey

Abbreviation	Term
SI	standard international
SOC	system organ class
SOP	standard operating procedure
ULN	upper limit of normal
WHO Drug	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment

INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. Study TV48125-CNS-30058, (a multicenter, double-blind, double-dummy study to explore the long-term safety and efficacy of TEV-48125 for the prevention of cluster headache), and was written in accordance with GSD-SOP_702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the clinical study report.

1. STUDY ENDPOINTS

1.1. Primary Objective and Endpoints

The primary objective of this study is to evaluate the long-term safety of fremanezumab in adult patients with cluster headache (CH).

Safety endpoints are as follows:

- occurrence of adverse events throughout the study
- changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results
- changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in vital signs (pulse, systolic and diastolic blood pressure, and oral temperature) measurements

  Note: Oxygen saturation will be measured in cases of suspected anaphylaxis and severe hypersensitivity. Respiratory rate will also be measured in these cases but not as a standard vital sign.
- abnormal standard 12-lead electrocardiogram (ECG) findings
- clinically significant changes in physical examination, including body weight
- occurrence of injection site reactions (ie, erythema, induration, and ecchymosis) and/or injection site pain
- occurrence of anaphylaxis and hypersensitivity reactions
- use of concomitant medications during the study
- suicidal ideation and behavior as measured by the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

1.2. Secondary Objective and Endpoints

There are no secondary objectives and secondary endpoints in this study.

1.3. Immunogenicity Objective and Endpoints

The immunogenicity objective is to evaluate the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to fremanezumab.

The immunogenicity endpoints are ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities).

1.4. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are:

- [redacted]

[redacted]

[redacted]

2. STUDY DESIGN

2.1. General Design

This is a 68-week extension study to evaluate the long-term safety and efficacy of fremanezumab in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed.

Upon completion of the final study assessments, early withdrawal from the study, or discontinuation for any reason, patients will be offered the opportunity to enter a 32-week long-term safety study (as described in the study protocol of TV48125-CNS-30058) for safety and ADA evaluation without additional dosing. Patients who satisfactorily complete the study may be offered to enroll the long-term safety study TV48125-CNC-30058 for 68 weeks (as described in the study protocol) to receive additional dosing and a final follow-up visit for safety and ADA evaluation. In any case, during the period of the long-term safety study, where patients are not receiving additional dosing (and are waiting for ADA evaluation), these patients should be treated with standard of care as appropriate.

It was planned that 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study,

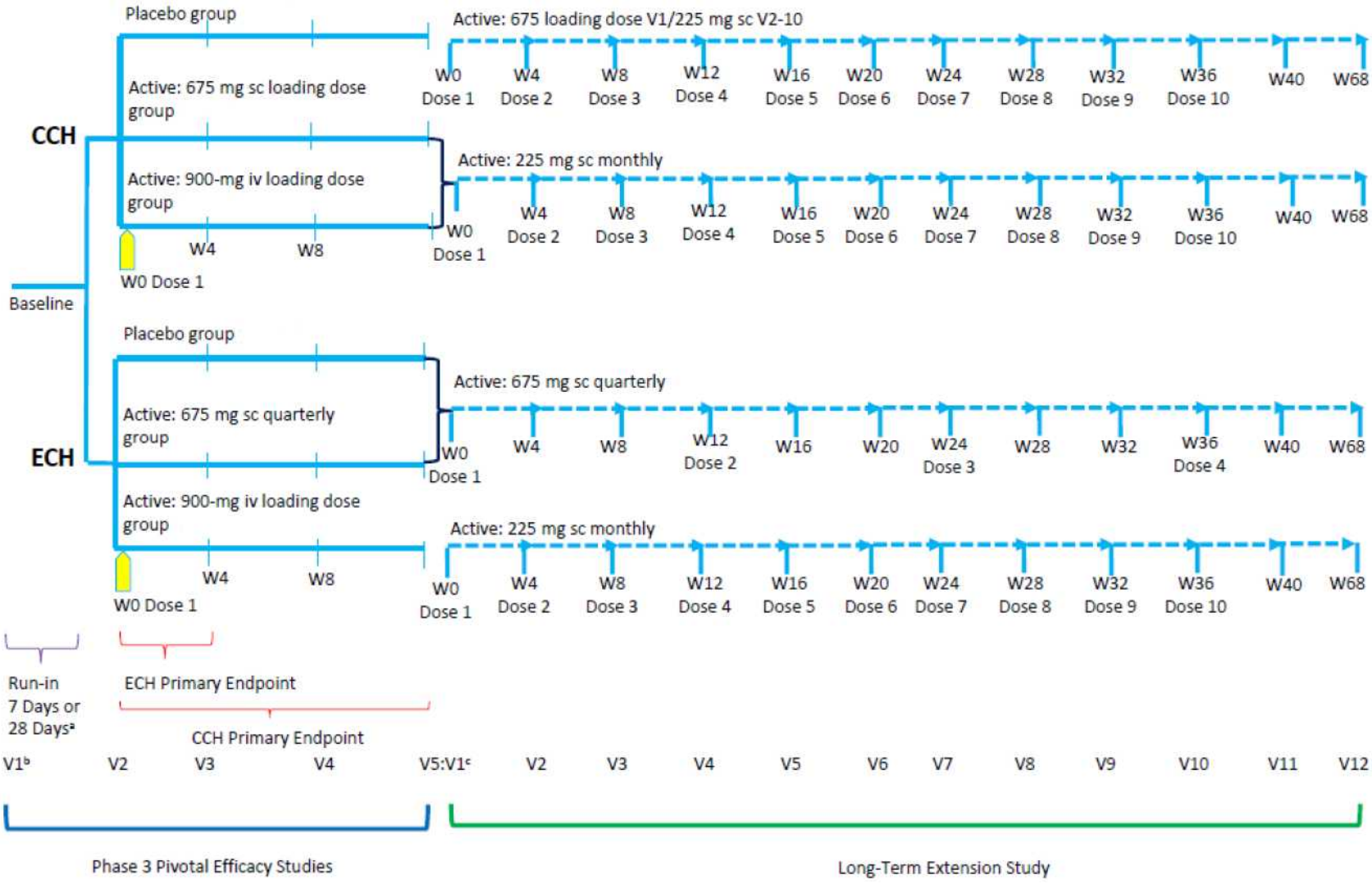
The end of study is defined as the date the last patient attends the follow-up visit.

The study duration will be for approximately 42 months from Q1/2017 to Q2/2020. Note, the study is completed Q2/2019 due to early terminations of pivotal Studies TV48125-CNS-30056 and TV48125-CNS-30057.

The study schematic diagram for patients enrolling in this study for the purpose of evaluating the long-term safety and efficacy of fremanezumab is presented in Figure 1.

Study procedures and assessments with their timing are summarized in Table 4 of the study protocol (patients enrolling in this study from the pivotal efficacy studies) and Table 5 of the study protocol (patients rolling over from the pivotal efficacy studies for evaluation of ADAs, adverse events, and concomitant medications only).

Figure 1: Overall Study Schematic Diagram



[a] The run-in period for patients with ECH lasted at least 7 days (+3 days), and the run-in period for patients with CCH lasted at least 28 days (+3 days).
[b] Screening will occur at visit 1 of the Phase 3 pivotal efficacy studies.
[c] Visit 1 of this study corresponds to the EOT visit (visit 5) of the pivotal efficacy studies. The EOT visit procedures/assessments for the pivotal efficacy study must be completed before beginning visit 1 procedures/assessments. EOT visit procedures/assessments will not be repeated at visit 1 of this study. The EOT visit procedures/assessments are detailed in the protocols for Studies TV48125-CNS-30056 and TV48125-CNS-30057.

CCH=chronic cluster headache; ECH=episodic cluster headache; EOT=end-of-treatment; iv=intravenous; pts=patients; sc= subcutaneous; V=visit; W=week.

Note: Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study.

[redacted]

2.2. Randomization and Blinding

This is a double-blind study; blinding will be retained from the pivotal studies and throughout this long-term safety extension study. Patients will be assigned to treatments as described in Table 1 and Section 5.1.1.1 of the study protocol based on their randomization in the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057).

2.3. Data Monitoring Committee

Not applicable.

2.4. Sample Size and Power Considerations

There are no statistical considerations for the sample size. Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study.

[redacted]

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

Not applicable.

2.5.2. Final Analyses and Reporting

All analyses identified in this SAP will be performed after the final database lock for study completion. The study will be unblinded after the pivotal studies (TV48125-30056 and TV48125-30057) are completed and unblinded.

3. ANALYSIS SETS

3.1. Enrolled Patients

The enrolled patients will include all patients who are enrolled in the study for any reason.

3.2. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all patients who are enrolled in this study for additional fremanezumab treatment and long-term safety evaluation, regardless if they receive study treatment or not.

This analysis set does not include patients who are enrolled in this study for the evaluation of ADA and safety only.

3.3. Safety Analysis Set

The safety analysis set will include all patients who receive any dose of IMP.

[redacted]

[redacted]

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include count (n), mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. In addition, for fremanezumab concentration percentage coefficient of variation (%CV) and geometric mean will also be calculated. Descriptive statistics for categorical variables include patient counts and percentages, and a missing category will be displayed as appropriate.

Summaries of potentially clinically significant abnormal values for clinical laboratory tests and vital signs values will include all postbaseline values (including scheduled, unscheduled, and early withdrawal visits).

4.2. Specification of Baseline Values

Baseline values will be the baseline values from the pivotal studies for both safety [redacted] analyses.

4.3. [redacted]

4.4. Study Days and Visits

For by-visit summaries, if there are multiple assessments at a postbaseline visit then the last non-missing assessment at that visit will be used for the summary (this includes scheduled and unscheduled assessments), except for triplicate ECG assessments (see Section 8.11 for further details).

Study visits for patients who are enrolled the study for full study assessments are in Table 2. Study procedures and assessments are detailed in the Table 4 of the study protocol.

Table 2: Study Visits for Treated Patients

	Double-blind treatment period											Follow-up period
Visit #	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40 EOT/early withdrawal**	**68**

Notes: Visit 1 of the current study corresponds with the EOT visit (visit 5) of the pivotal efficacy studies. The EOT visit procedures/assessments are detailed in the protocols for Studies TV48125-CNS-30056 and TV48125-CNS-30057. EOT=end of treatment.

Study visits and assessments for patients who are enrolled in the study for the purpose of evaluating ADAs and safety only are detailed in Table 3.

Table 3: Study Visits and Assessments for Patients Enrolled in the Study for Evaluation of Antidrug Antibodies and Safety (Adverse Events and Concomitant Medications) Only

Procedures and assessments	Enrollment visit	Follow-up visit
	Visit 1[a]	Visit 12
	Day 0	Approximately 7.5 months (approximately 5 half-lives of the IMP) after the last dose of the IMP during the pivotal efficacy study
Informed consent	X	
Adverse events[b]	X	X
Concomitant medication inquiry	X	X
Blood sample for ADA analysis		X

[a] Visit 1 of the current study corresponds with the EOT visit/early withdrawal visit of the pivotal efficacy studies. EOT visit procedures/assessments must be completed before the patient begins participation in this study. The EOT visit procedures/assessments are detailed in the protocols for Studies TV48125-CNS-30056 and TV48125-CNS-30057.

[b] Patients will return for unscheduled visits in the event of any safety concern.

ADA=antidrug antibody; EOT=end-of-treatment; IMP=investigational medicinal product.

'Last Assessment' may be derived for analysis purpose and is defined as the last observed postbaseline data. For patients who withdraw from the study, their data at the early withdrawal visit will be excluded from the by-visit sections but will be included in the Last Assessment section.

Study days are numbered relative to the first day of the IMP administration in this study. The start of treatment (day 1) is defined as the date on which a patient takes the first dose of the IMP in this study, as recorded on the case report form (CRF). Days will be numbered relative to treatment start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the first day of the IMP administration and day –1 being the day before the first day of the IMP administration).

5. STUDY POPULATION

5.1. General

The ITT analysis set (see Section 3.2) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment groups and overall. Treatment groups are

- **Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36**
  Note: for patients in 900 mg iv loading dose group from both Study TV48125-CNS-30056 and TV48125-CNS-30057 and patients in 675-mg sc loading dose group from Study TV48125-CNS-30057
- **Fremanezumab at 675 mg sc quarterly (approximately every 12 weeks) through week 36**
  Note: for patients in 675 mg sc and placebo group from Study TV48125-CNS-30056
- **Fremanezumab 675-mg sc loading dose followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg sc through week 36**
  Note: for patients in placebo group from Study TV48125-CNS-30057

In addition, summaries will be presented by indication (Episodic CH [patients from TV48125-CNS-30056] and Chronic CH [patients from TV48125-CNS-30057]) and the treatment groups.

5.2. Patient Disposition

Data from patients screened; patients screened but not enrolled and reason for not enrolled; patients who are enrolled; patients enrolled for ADA only; patients in ITT analysis set (enrolled for treatment), patients in ITT analysis set but not treated; patients in the safety and other analysis sets; patients who complete the treatment; patients who did not complete the treatment and reason; patients who complete the study; patients who withdraw from the study early and the reason will be summarized using descriptive statistics.

[redacted].

The summary will be presented for all patients.

5.3. Demographics and Baseline Characteristics

Patient's demographics and baseline characteristics data including age, age group (<40 years or ≥40 years), gender, race, race group (white or other), ethnicity, region (US/Canada or other), baseline weight (kg), baseline height (cm), baseline body mass index (kg/m^2), and preventive medication use (yes or no) at screening will be summarized using descriptive statistics for all analysis sets.

Baseline weight, baseline height, and baseline body mass index are the same baseline values in the pivotal studies, the last observed data before the administration of the first dose of the IMP in the pivotal study.

Data for ADA only patients will also be presented separately.

5.4. Medical History

Medical history refers to data collected in the pivotal studies.

All medical history abnormalities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Patients are counted only once in each SOC and only once in each preferred term.

Data for ADA only patients will also be presented separately.

5.5. Prior Therapy and Medication

Prior medications will include all medications taken prior to the administration of the first dose of the IMP in the pivotal studies.

All prior medications or therapy will be coded using the World Health Organization Drug Dictionary of medical codes (WHO Drug). The incidence of prior medications or therapy will be summarized by therapeutic class and preferred term using descriptive statistics. Patients are counted only once in each therapeutic class category, and only once in each preferred term category.

The prior medications will be summarized by the following indications categories:

- preventive medication from Appendix H of the study protocol for CH
- preventive medication from Appendix H of the study protocol for other reason than CH
- butalbital for CH
- butalbital for other reason than CH
- triptans for CH
- triptans for other reason than CH
- ergots for CH
- ergots for other reason than CH
- non-steroidal anti-inflammatory drugs (NSAIDs) for CH
- NSAIDs for other reason than CH
- opioids for CH
- opioids for other reason than CH
- other

Data for ADA only patients will also be presented separately.

5.6. Childbearing Potential and Methods of Contraception

Information related to reproductive system findings will be collected at visit 1. Data will be listed.

5.7. Physical Examinations

Patients with at least 1 abnormal finding (overall) and abnormal findings for each category will be summarized.

5.8. Study Protocol Deviations

Data from patients with any important protocol deviations during the study will be summarized overall and for each category using descriptive statistics.

[redacted]

6.4.1. [redacted]

6.4.2. [redacted]

6.4.3. [redacted]

6.4.4. [redacted]

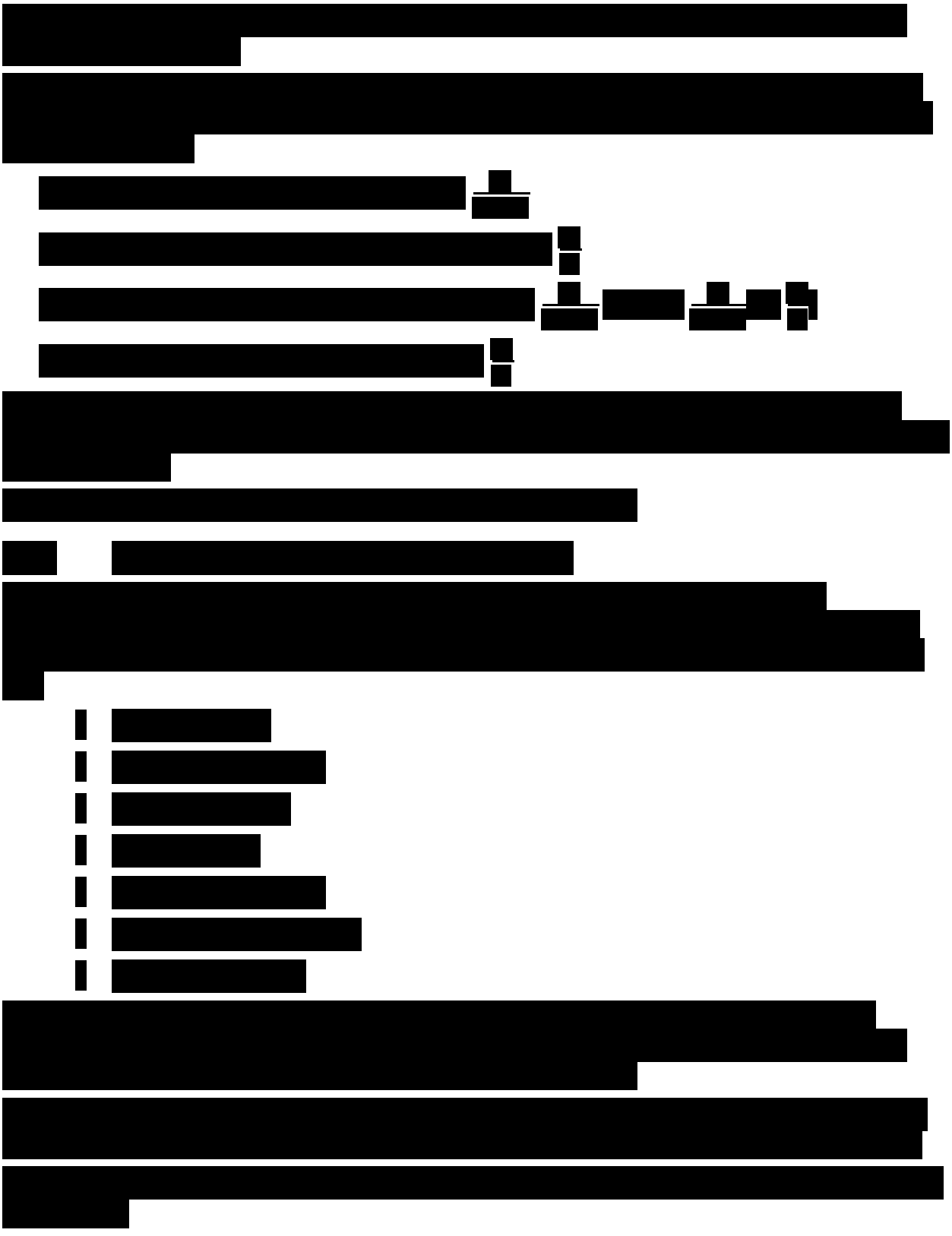
6.4.4.1. [redacted]

[redacted]

6.4.4.2. [redacted]

[redacted]

[redacted]



[redacted]

7. MULTIPLE COMPARISONS AND MULTIPLICITY

No inferential analysis will be performed in this study.

8. SAFETY ANALYSIS

8.1. General

The safety analysis set will be used for all safety analyses unless otherwise specified. Summaries will be presented by treatment groups as actually received and overall. In addition, summaries will be presented by indication (Episodic CH [patients from TV48125-CNS-30056] and Chronic CH [patients from TV48125-CNS-30057]) and the treatment groups.

8.2. Duration of Exposure to Study Drug

Study IMP will be administrated visit 1 through visit 10 with three treatment groups as follows:

- **Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36**
  Note: for patients in 900 mg iv loading dose group from Study TV48125-CNS-30056 or TV48125-CNS-30057 and patients in 675-mg sc loading dose group from Study TV48125-CNS-30057
- **Fremanezumab at 675 mg sc quarterly (approximately every 12 weeks) through week 36**
  Note: for patients in 675 mg sc and placebo group from Study TV48125-CNS-30056
- **Fremanezumab 675-mg sc loading dose followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg sc through week 36**
  Note: for patients in placebo group from Study TV48125-CNS-30057

There are total 10 dosing visits (see Figure 1). Patients will receive either injection(s) of test IMP or injection(s) of placebo IMP at each visit.

Duration of treatment (days) and number of doses (≥1 dose, ≥2 doses, ≥3 doses, . . ., 10 dose) will be summarized using descriptive statistics.

[redacted]

IMP administration and accountability data will be listed.

8.3. Adverse Events

Adverse events will be recorded from time informed consent is obtained through the end of study participation.

The following are considered protocol-defined adverse events of special interest to be sent to the sponsor's Global Patient Safety and Pharmacovigilance Department for evaluation: ophthalmic-related adverse events of at least moderate severity, events of possible drug-induced liver injury (aspartate aminotransferase or alanine aminotransferase ≥3 × the upper limit of

normal [ULN], total bilirubin ≥2 × the ULN, or international normalized ratio >1.5), Hy's Law events, or events of anaphylaxis and severe hypersensitivity reactions.

All adverse events will be coded using MedDRA (version 18.1). Each patient will be counted only once in each preferred term or SOC category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Adverse events with the missing flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non-serious adverse events.

Summaries for injection site adverse events and protocol-defined adverse events of special interest will be presented (overall and by severity).

Listings for deaths, serious adverse events, adverse events leading to discontinuation, injection site adverse events, and protocol-defined adverse events of special interest will be presented. In addition, listings for MedDRA dictionary terms for adverse event descriptions and adverse event preferred terms by patient number and treatment group will be presented.

Spontaneous abortion or an elective abortion due to developmental anomalies will be reported as a serious adverse event (protocol Section 7.2). These serious adverse events will be listed separately if applicable.

Summaries will include treatment-emergent adverse events which are defined as adverse events occurring at or after the first dose of the IMP. The listing will include all adverse events recorded.

Adverse events for patients who did not meet screening criteria will be listed.

Adverse event (overall) will also be presented for ADA only patients.

8.4. Injection Site Assessments

Injection site assessments will be performed immediately (+10 minute) and 1 hour (±15 minutes) after receiving each dose of the IMP visits 1 through 10. The injection sites will be assessed for erythema, induration, and ecchymosis. More details are in Section 7.11 of the study protocol.

Injection-site reactions should be recorded as adverse events. Injection-site related adverse events will be summarized as indicated in Section 8.3.

8.5. Hypersensitivity/Anaphylaxis

Patients will be assessed for suspected anaphylaxis reaction during and after administration of the IMP (through 1 hour postdose) at visits 1 through 10. Data will be summarized using descriptive statistics.

The number of patients with suspected anaphylaxis reactions and number of suspected anaphylaxis reactions per patient will be summarized using descriptive statistics.

The relative time of suspected event will be calculated as date/time of suspected event - date/time of most current IMP administration and summarized using descriptive statistics. If a patient has more than one suspected anaphylaxis reactions, the earliest time will be used for the calculation.

Data will be listed.

8.6. Electronic Columbia Suicide Severity Rating Scale

The eC-SSRS Since Last Visit version will be completed by the patient at visits 2 through 12, including unscheduled visits. Any positive findings on the eC-SSRS 'Since Last Visit' version requires evaluation by a physician or doctoral-level psychologist.

Data for patients with positive findings (having suicidal ideation or suicidal behavior) will be listed.

8.7. Deaths

If any patient dies during the study, all relevant information will be discussed in the patient narrative included in the clinical study report.

8.8. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis; see protocol Appendix M) will be performed at visits 4, 7, 10 and 11 using the central laboratory. All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2 of the protocol.

Laboratory test results will be presented in standard international (SI) units in summaries. Laboratory values and changes from baseline to each visit and Last Assessment will be summarized using descriptive statistics. Shifts (below [low], within [normal], and above [high] the normal range) from baseline to each postbaseline visit and the Last Assessment will be summarized using patient counts. Baseline is defined as the last observed data before the administration of the first dose of the IMP in the pivotal study.

The potentially clinically significant abnormal values will be derived using criteria specified in Table 4 based on all postbaseline values (including scheduled, unscheduled, and withdrawal visits). The overall incidence of potentially clinically significant abnormal values will be summarized for laboratory variables using descriptive statistics by treatment group. Listings for patients who have potentially clinically significant abnormal laboratory data will be presented.

Table 4: Criteria for Potentially Clinically Significant Laboratory Values

Test		Criterion value
Serum chemistry		
ALT		≥3x ULN
AST		≥3x ULN
ALP		≥3x ULN
GGT		≥3x ULN
LDH		≥3x ULN
BUN		≥10.71 mmol/L
Creatinine		≥177 μmol/L
Bilirubin (total)		≥34.2 μmol/L
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L
	Women	≤95 g/L
WBC counts		≤3 x 10^9/L ≥20 x 10^9/L
Eosinophils		≥10%
ANC		≤1 x 10^9/L
Platelet counts		≤75 x 10^9/L ≥700 x 10^9/L
Urinalysis		
HGB		≥2 unit increase from baseline
Glucose		≥2 unit increase from baseline
Ketones		≥2 unit increase from baseline
Total protein		≥2 unit increase from baseline

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma- glutamyl transpeptidase; HGB=hemoglobin; LDH=lactate dehydrogenase; RBC=red blood cell; ULN=upper limit of normal range; WBC=white blood cell

Serum beta-human chorionic gonadotropin (β-HCG) tests will be performed for all women of childbearing potential at visit 11. Urine β-HCG tests will be performed for women of childbearing potential at visits 1 through 10. Positive pregnancy test results will be listed.

Currently menstruating (yes, no, n/a) information will be collected from each female patient prior to blood and urine collection for clinical laboratory tests. Data will be listed.

8.8.1. Laboratory Values Meeting Hy's Law Criteria

All occurrences of possible drug-induced liver injury that meet Hy's law criteria as defined in the Section 7.1.5.1 of the study protocol will be included in serious adverse events reporting.

8.9. Physical Examinations

Physical examinations will be performed at visits 2, 4, 5, 7, 8, 10, 11, and 12. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2 of the study protocol.

Abnormal physical examination findings will be listed.

Weight will be summarized and listed with vital signs data.

8.10. Vital Signs

Vital signs (pulse, systolic and diastolic blood pressure, and body temperature) will be measured at each (visit 2 through 12). Weight will be measured at visits 2, 4, 5, 7, 8, 10, 11, and 12. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2 of the protocol.

Vital signs (including weight) values and changes from baseline to each visit and the Last Assessment will be summarized using descriptive statistics. The incidence of potentially clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics. Baseline is defined as the last observed data before the administration of the first dose of the IMP in the pivotal study.

Table 5 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column. The potentially clinically significant abnormal vital signs values will include all postbaseline values (including scheduled, unscheduled, and early withdrawal visits) for the summaries.

Table 5: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15 bpm
	≤50 bpm	Decrease of ≥15 bpm
Systolic blood pressure	≥180 mm Hg	Increase of ≥20 mm Hg
	≤90 mm Hg	Decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15 mm Hg
	≤50 mm Hg	Decrease of ≥15 mm Hg
Temperature	≥38.3°C	Change of ≥1.1°C

bpm=beats per minute

8.11. Electrocardiography

Triplicate 12-lead ECGs will be collected at visits 4, 7, 10 and 11. Any ECG finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2 of the protocol.

For ECG variables, the mean of recorded results from the 3 measurements at a visit will be calculated. The mean results and mean changes from baseline to each visit and Last Assessment will be summarized using descriptive statistics. Baseline is determined based on the last set of observed data before the administration of the first dose of the IMP in the pivotal study.

For ECG findings, the worst value of recorded findings at a visit will be used for analysis. Baseline ECG findings and shifts (normal, abnormal not clinically significant, and abnormal clinically significant) from baseline to overall (worst value for a patient) and the Last Assessment (worst value of recorded findings from the last visit) will be summarized using patient counts.

8.12. Concomitant Medications or Therapies

Concomitant medications, treatments, or procedures will be collected up to the end of study.

All concomitant medications will be coded using the WHO Drug. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. The concomitant medications will include all medications taken after administration of the first IMP.

The subset of medications or therapies will be summarized by the indication categories as indicated in Section 5.5.

Concomitant medications for patients who are enrolled in this study for the evaluation of ADA only will be listed.

9. TOLERABILITY VARIABLES AND ANALYSIS

Tolerability was not specifically defined for this study.

10. PHARMACOKINETIC ANALYSIS

There are no prespecified pharmacokinetic endpoints.

Summary of plasma concentration of the study drug will be based on the safety population and will be presented by visit for each of the indication (CCH or ECH) and active treatment groups (and the treatment received in 056 and 057 studies). The plasma concentration will be listed by indication, active treatments, scheduled visits, and time points.

11. PHARMACOGENOMIC ANALYSIS

Pharmacogenomic analysis results will be summarized for each gene tested. An attempt will be made to correlate clinical observations (pharmacokinetics, safety, efficacy, or other effects) with the genotypes observed. Additional pharmacogenomic analysis may be conducted at a later time and will be reported in a separate addendum report.

This analysis is not included in this SAP.

12. BIOMARKER ANALYSIS

Biomarker analysis will include logistic regression, receiver operating characteristic curves, and summary statistics. This analysis will be reported separately. Measurements will be made using validated assays.

This analysis is not included in this SAP.

13. IMMUNOGENICITY ANALYSIS

A summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. The impact of immunogenicity on the pharmacokinetic profile, IMP efficacy, and clinical safety will be evaluated. This ADA impact analysis will be reported separately.

This analysis is not included in this SAP.

14. [redacted]

15. PLANNED INTERIM ANALYSIS

Not applicable.

16. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS®.

17. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

None.

18. REFERENCES

[redacted] U.S.A.

APPENDIX A. [redacted]

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APPENDIX B. [redacted]

APPENDIX C. [redacted]

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Self-Care

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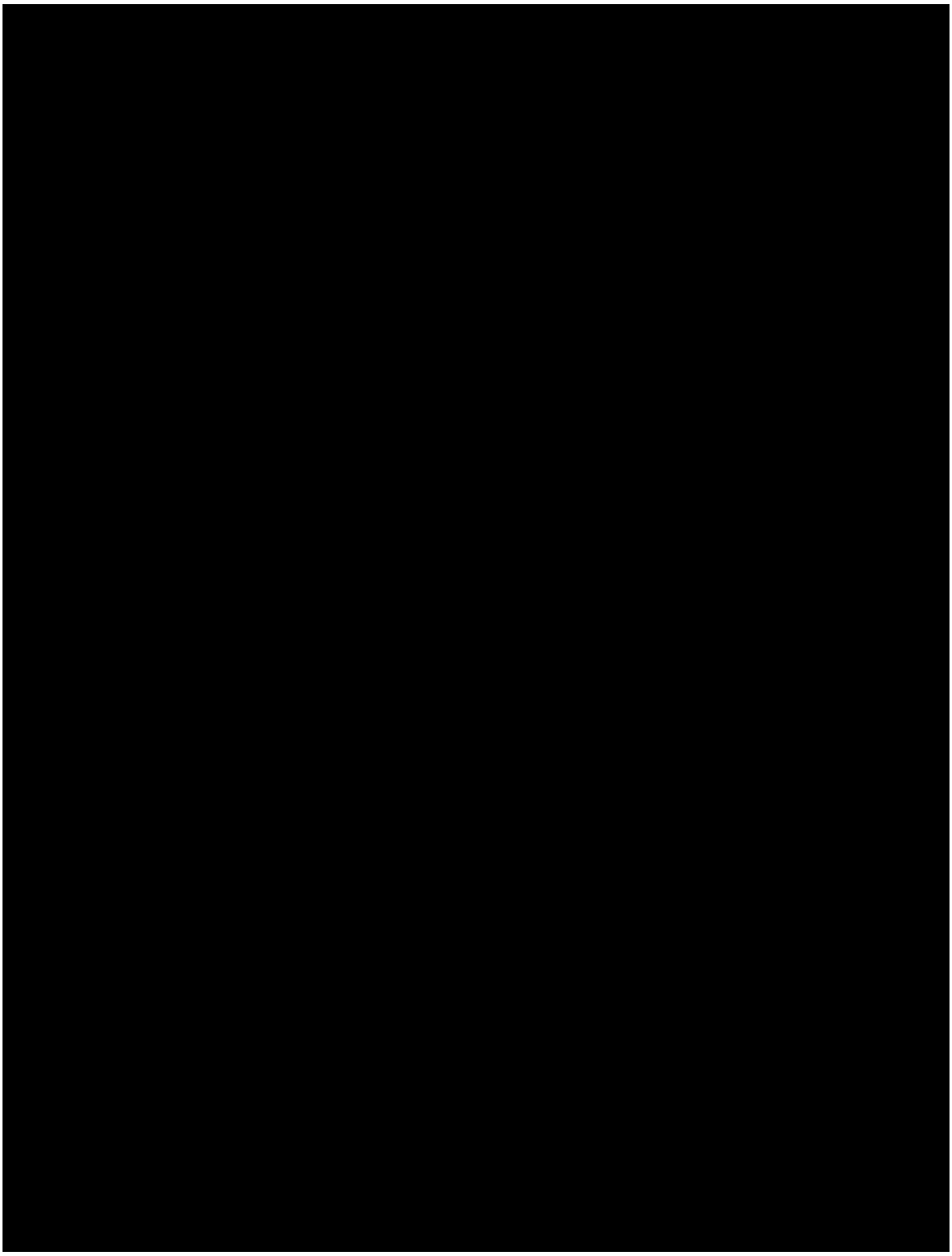

APPENDIX D. [redacted]

D	A	Question/Response	D	A	Question/Response
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Scoring:

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APPENDIX E. [redacted]

Scale	Label	Item#	Question	Response
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Scale	Label	Item#	Question	Response
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APPENDIX F. [redacted]

Question (baseline visit)	Response
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Question (baseline visit)	Response
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[redacted]	[redacted]

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APPENDIX G. [redacted]

Question (at baseline visit)	Response
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Question (at baseline visit)	Response
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APPENDIX H.

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