Click Therapeutics

Statistical Analysis Plan (SAP)
Version 1

Protocol CT-132-R-001 Amendment 3

A Randomized Double-blind, Digital-Controlled, Parallel-Group, Virtual Study to Evaluate the Effectiveness and Safety of a Digital Therapeutic (CT-132) as Adjunctive Therapy in Late Adolescents and Adults for the Prevention of Episodic Migraine

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
App	Application (software)
CI	Confidence Interval
[redacted]	[redacted]
CT-132	A novel prescription digital therapeutic that is being developed by Click Therapeutics that delivers an interactive, software-based intervention for prevention of migraine.
eDiary	electronic Diary
EDC	Electronic Data Collection
[redacted]	[redacted]
HFEM	High Frequency Episodic Migraine
ICF	Informed Consent Form
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LFEM	Low Frequency Episodic Migraine
LSM	Least Squares Means
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MHD(s)	Monthly Headache Day(s)
MIDAS	Migraine Disability Assessment
MI	Multiple Imputation
mITT	Modified Intent-to-Treat
MMD(s)	Monthly Migraine Day(s)
MNAR	Missing Not at Random
MSQ	Migraine-Specific Quality-of-Life Questionnaire
[redacted]	[redacted]
PGI-C	Patient Global Impression of Change
PMM	Predictive Mean Matching
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VLFEM	Very Low Frequency Episodic Migraine

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis for Click Therapeutics study CT-132-R-001, “A Randomized Double-blind, Digital-Controlled, Parallel-Group, Virtual Study to Evaluate the Effectiveness and Safety of a Digital Therapeutic (CT-132) as Adjunctive Therapy in Late Adolescents and Adults for the Prevention of Episodic Migraine”. This SAP should be read together with the protocol for full details on the study.

The SAP is intended to agree with the protocol with regard to statistical aspects that were specified in the protocol. However, the SAP may contain additional details for analyses that were defined in the protocol, and may provide details on statistical aspects that were not described in the protocol. In case of disagreement between the SAP and the protocol, the SAP prevails. Differences will be described in the statistical report and at the end of this document.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Study Objectives

The study objectives are to evaluate the effectiveness and safety of CT-132 in reducing the number of monthly migraine days (MMDs), compared with a Digital Control, among late adolescents and adults with migraine.

The study endpoints to support these objectives are listed in Section 3.

2.2. Primary Estimand

The primary estimand will be the effect of the digital therapeutic (CT-132) on number of MMDs regardless of use of prohibited medications, adherence to treatment or early termination for any reason.

This estimand considers the following intercurrent events:

- Use of prohibited medications
- Lack of adherence
- Early discontinuation due to any reason

Since participants may use their prescribed medication to treat episodic migraine (including changes in medication or dosage) as needed while continuing to use the Study App, and since the study population is defined as participants diagnosed with migraine and taking first- and second-line preventive medications, the use of these medications is not considered an intercurrent event.

Attributes of the primary estimand:

- The **treatment condition** of interest is CT-132 compared to a digital control, both alongside prescribed medications, to treat episodic migraine
- The **population** is late adolescents and adults with episodic migraine who fulfill all of the inclusion criteria and none of the exclusion criteria for the study
- The **endpoint** to be considered is the change from baseline (28-day run-in period) in MMDs to week 12 (previous 28 days, Weeks 9-12)
- The **population-level summary** is the least squares mean (LSM) difference between CT-132 and the digital control

Strategies for Addressing Intercurrent Events in Primary Estimand

- Use of prohibited medications: In case of use of prohibited medications, participants will be discontinued from the study and the Study App will be disabled for them. Data accumulated until the Study App is disabled will be included in the analysis. This approach complies with the treatment policy strategy.
- Lack of adherence: The treatment effect of CT-132 will be estimated regardless of lack of adherence to lessons and activity. This approach complies with the treatment policy strategy.

- Early discontinuation due to any reason: The treatment effect of interest is regardless of early discontinuation of treatment which complies with the treatment policy strategy. For that reason, data that does not exist after early discontinuation will be considered as missing data, and will be imputed as described in Section 6.3.

3. STUDY ENDPOINTS

Unless otherwise specified, effectiveness endpoints will be evaluated as a comparison between the CT-132 treatment group and the digital control group.

3.1. Primary Effectiveness Endpoints

Change in the number of MMDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week12).

3.2. Secondary Effectiveness Endpoints

- Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MMDs to Week 12 (previous 28 days, Week 9 through Week12).
- Change from baseline (28-day run-in period) in the number of MMDs recorded over the previous 28 days at Week 4 and at Week 8.
- Change from baseline (28-day run-in period) in the mean number of MMDs over 12 weeks.
- Change in the number of headaches with at least moderate severity from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12).
- Change from baseline (28-day run-in period) in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score over the previous 28 days at Week 4, Week 8, and Week 12.
- Change from baseline (28-day run-in period) in the Migraine Disability Assessment (MIDAS) to Week 12 (previous 28 days, Week 9 through Week 12).
- Change from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12) in the number of migraines with use of an acute medication.
- Change in the number of MHDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12).

3.3. Exploratory Endpoints

- [redacted]
- Monthly headache days (MHDs):
    - Change from baseline (28-day run-in period) in the number of MHDs recorded over the previous 28 days at Week 4 and at Week 8.

  - Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MHDs at Week 12 (previous 28 days, Week 9 through Week12).
  - Change from baseline (28-day run-in period) in the mean number of MHDs over 12 weeks. .
- Patient Global Impression of Change (PGI-C) score at Week 12.
- Shift from High Frequency Episodic Migraine (HFEM) at baseline (28-day run-in period) to Very Low Frequency Episodic Migraine (VLFEM) or Low Frequency Episodic Migraine (LFEM) at Week 12 (previous 28 days, Week 9 through Week 12).

3.4. Safety Endpoints

- Frequency and severity of Adverse Events (AE), serious AEs (SAE), and discontinuation from the study due to AEs.
- Frequency and severity of AEs related to the worsening of migraine.

4. STUDY DESIGN

4.1. General Design

This is a randomized, double-blind, digital-controlled, parallel-group, virtual study to assess the effectiveness and safety of CT-132 in late adolescents and adults for the prevention of migraine in comparison to a digital control. Eligible participants must report having four or more migraine days per month in the three months prior to the Screening Visit. All participants will complete an identical, pre-randomization onboarding experience, which includes verifying participant understanding of and interest in the study, and a run-in period to capture baseline MMDs within the Study App. During the run-in period and intervention period, these participants will continue to take their healthcare provider-prescribed acute and first- and second-line preventive medications for the treatment of migraine, while continuing to use the Study App to report headache and symptoms and medications. This daily reporting is referred to below as eDiary use. Upon successful completion of the onboarding experience, run-in period, and confirmation of participant interest and eligibility, the participant will be randomized at the baseline study visit. The duration of participation will be approximately 19 weeks, including an up-to-14-day screening period, a 28-day run-in period, a 12-week double-blind intervention period, and an up-to-7-day follow-up period for safety assessments.

The activities and assessments during the 2-week screening period, the 4-week run-in period, the 12-week double-blind intervention period, and the 1-week follow-up period will be completed according to the Schedule of Activities and Assessments (Protocol Section 1.2). Trial staff will implement procedures remotely. Participants will be assessed based on validated standard clinician-rated and participant-rated outcome scales for migraine at screening, the intervention period, and the follow-up period. Participants will also be evaluated for safety throughout the duration of the trial.

4.2. Sample Size and Power Considerations

Assuming a difference of 1.6 in the mean MMDs between the two arms, and a common standard deviation (SD) of 5.8, 474 participants are required for the study (237 per arm) to ensure 85% power and using a two-sided alpha of 5%. Sample size was calculated using a two-sample *t*-test assuming equal variance. Assuming 15% drop out, at least 558 participants will be randomized in a 1:1 ratio to CT-132 or digital control.

4.3. Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). The IWRS will be integrated into the electronic data collection (EDC) system. Study team(s) will refer to the randomization information in the EDC system.

Participants will be randomly assigned in a 1:1 ratio to receive either CT-132 or the digital control as study intervention through the Study App. Investigators and designated personnel will remain blinded to each participant's assigned study intervention throughout the course of the study.

Study participants will be blinded to the effectiveness hypothesis of the study. Both treatment arms will be presented to the participant as possible treatments for migraine. No references to CT-132

or digital control will be made to the participant. This approach limits the risk of participant unblinding to treatment assignment and expected effectiveness.

4.4. Planned Timing of Analysis

Final analysis will be performed after all participants have completed the study, the SAP is finalized, and database is locked and study is unblinded.

5. ANALYSIS SETS

5.1. Consented Analysis Set

The Consented Analysis set includes all participants who signed the Informed Consent Form (ICF).

5.2. Enrolled Analysis Set

The Enrolled Analysis set includes all participants who signed the ICF and completed the run-in period.

5.3. Intention-to-Treat (ITT) Analysis set

The ITT set includes all enrolled participants who were randomized, based on the assigned intervention in the randomization and recorded in the database, regardless of treatment by Study App intervention. This will be the main analysis set for all effectiveness analyses.

5.6. Safety Analysis set

The safety analysis set includes all randomized participants who are exposed to the study intervention (completed at least one task). Participants will be analyzed according to the intervention they received. This analysis set will be used for all safety analyses.

6. STATISTICAL CONSIDERATIONS

6.1. General

For continuous variables, summary tables will provide the number of observations [n], mean, standard deviation, median, minimum, and maximum. For categorical variables, summary tables will provide the number of observations [n] and frequency of each category (including missing data). Tabulations will be presented by treatment and overall, when appropriate. Modelling and testing will be described for each endpoint.

Study day for specific measurement is calculated as (date – date of baseline visit). Run-in period will include study days -28 until -1. Day 0 is the baseline day and days >=1 are treatment period days.

Measurements taken at Early Termination visit/withdrawal will be presented in listings but will not be included in summaries and analyses.

6.2. Specification of Baseline Values

A participant's baseline MMDs/MHDs will be the total number of headache/migraine days recorded during the 28-day run-in period. Baseline MMDs is a subset of baseline MHDs.

For endpoints not mentioned above, a baseline value is the latest value measured during the baseline visit or prior to baseline visit.

6.3. Handling of Missing Data

Participants should complete the eDiary on a daily basis during the 28 days of the run-in period and the 12 weeks of treatment. In the eDiary, the participants report whether they experienced a headache during that day including the start and end time, symptoms, and usage of acute medications. The eDiary allows for retrospective reporting of headaches up to 48 hours.

[redacted]

[redacted]

[redacted]

[redacted]

7. STUDY POPULATION

7.1. Participant Disposition

This analysis will be done on the consented analysis set.

The number of participants who were screened, completed the run-in period, and were randomized into the study will be presented. The number of participants who started treatment, and number of participants who discontinue the study will be presented by reason for discontinuation. The number of participants in the consented, enrolled, ITT, mITT, PP, and safety analysis sets will be presented.

7.2. Demographics and Baseline Characteristics

In order to assess the comparability of the two arms at baseline, demographic and baseline characteristics data will be summarized by treatment group.

[redacted]

A summary table will be generated and will include sex, age (continuous and by age category), ethnicity, race, geographical region, income level, level of education, baseline MMDs (using the observed data), baseline MHDs (using the observed data), Low and High frequency episodic migraine classification at baseline, participant's current prescription migraine medications at baseline (acute only; preventive L1 with or without acute; preventive L2 with or without acute medications; other), baseline MSQ, baseline PHQ-8, baseline GAD-7 and baseline MIDAS.

Participants will be assigned to a race category according to their response. Participants who responded to the question about race with more than one race category will be assigned to the "Multiple" category.

7.3. Medical History and Medications

The medical history and medication analysis will be performed using the ITT analysis set.

Medical history will be summarized and presented by treatment group.

The proportion of participants who received previous therapy will be summarized by WHOdrug preferred term and presented by treatment group. A separate summary will be presented for migraine medications taken prior to the study.

The proportion of patients who report concomitant medications during study treatment will be summarized by WHOdrug preferred term and presented by treatment group regardless of whether the medication was taken prior to baseline.

Previous therapy is defined as medication with end date earlier than the baseline date (study app activation).

Concomitant medication is defined as medication with an end date on or later than the baseline date (study app activation) or missing end date.

The proportion of participants who use acute migraine medication and preventive migraine medication will be summarized, separately, by WHOdrug preferred term and presented by treatment group.

7.4. Protocol Deviation

The protocol deviations will be documented in a deviation tracker and classified into major and minor deviations.

The number of protocol deviations and the proportion of subjects (%) with at least one deviation will be shown for the ITT set. The summary will include the deviation category (Informed Consent, Inclusion/Exclusion, etc.) and deviation severity (minor/major) and will be presented by treatment arm.

7.5. [redacted]

[redacted]

7.6. Exposure

Exposure to study intervention, in days, will be calculated for each participant as number of days from first day of treatment until last day of treatment + 1. First day of treatment is defined as the first date with adherence to task and last day of treatment is defined as the last date of adherent to task.

Exposure will be summarized using descriptive statistics by treatment group.

8. EFFECTIVENESS ANALYSIS

Unless otherwise specified, all effectiveness analyses will be conducted on the ITT set. For several endpoints, the analyses will be repeated for other analysis sets, as described for the relevant endpoints in the sections below.

For all endpoints, descriptive statistics will be presented by treatment group and by visit/weeks where applicable. Actual value and change from baseline (where applicable) will be presented.

Several endpoints are based on MMDs and MHDs. For details regarding qualification of headache as migraine please refer to Appendix A - Data Specifications in this document, Section 6.4. For details regarding derivation of MMDs please refer to Section 7 in this appendix. For details regarding derivation of MHD, please refer to Section 8 of this appendix.

8.1. Primary Effectiveness Endpoint and Analysis

8.1.1. Primary Effectiveness Endpoint

The primary endpoint is change in MMDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12).

Baseline MMDs will be calculated as the number of MMDs in the 28-day run-in period.

The Week 12 MMDs will be calculated as the number of MMDs in the 28 days during Weeks 9-12.

The change from baseline to Week 12 will be calculated as (Week 12 MMDs – baseline MMDs).

In case of missing eDiary days, the MMDs will be imputed as described in Section 6.3, resulting in 100 complete data sets.

8.1.2. Primary Hypotheses

The null hypothesis that will be examined for the primary effectiveness endpoint is that there is no difference in effectiveness between the CT-132 treatment arm and the control in regard to the change from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12) in MMDs:

H_0: $\mu\_CT132 = \mu\_DC$

H_1: $\mu\_CT132 \neq \mu\_DC$

Where μ_CT132 is the mean change from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12) in MMDs for the CT-132 treatment arm and μ_DC is the mean change from baseline (28-day run-in period) to Week 12 (previous 28 days, week 9 through Week 12) in MMDs for the digital control arm.

The success criterion for the study is rejection of the null hypothesis as defined above with a two-sided 0.05 alpha level.

8.1.3. Primary Effectiveness Analysis

An Analysis of Covariance (ANCOVA) model will be used to analyze the primary endpoint. The dependent variable is the change from baseline to Week 12 in MMDs for each participant.

The model will adjust for the following covariates: treatment arm, baseline MMDs, and baseline use of concomitant medications for prevention of migraine. The analysis will be conducted on the ITT analysis set.

Each of the 100 complete datasets will be analyzed using this model. Rubin's rule will be used to combine the results from each of the 100 analyses, resulting in LS mean for the treatments difference and *p*-value associated with the treatment effect. The 95% confidence interval (CI) for the treatment difference will also be constructed. This is considered as the primary analysis for the study, and the study will be considered successful if the p-value is less than 0.05.

LS means for the change from baseline, within each arm as well as the SE, 95% CI and *p-value* for the null hypothesis of no change from baseline versus the two-sided alternative will be presented.

8.2. Supportive Analyses

8.2.1. Non-parametric Analysis

The primary analysis described in Section 8.1.3 assumes that the primary endpoint is normally distributed. In order to evaluate the robustness for this assumption, Wilcoxon rank-sum test will be conducted on the primary endpoint, for each of the 100 complete datasets. The results from the 100 analyses will be pooled by extracting the variability for each dataset and then using Rubin's rule.

8.2.2. Responder analysis for different thresholds

In order to describe the magnitude of change within each treatment group in a different way than mean change in MMD, a summary table with descriptive statistics will show the proportion of participants, within each arm, with change from baseline (CFB) in MMDs for different response thresholds, ranging from CFB=0 to CFB=-7.

[redacted]

8.3. Sensitivity Analyses

8.3.1. Tipping Points Analysis

To evaluate the robustness of the results of the primary analysis to the MAR assumption, a tipping point analysis will be performed as follows:

This analysis consists of a series of analyses, using the same model as for the primary analysis, but using Missing Not at Random (MNAR) imputations instead of MAR, as defined in Section 6.3, [redacted] Under MNAR, assuming smaller and smaller treatment effects until the first time the statistical significance is lost, and study conclusions revert.

This point is considered the "tipping point". The treatment effect is then evaluated for its plausibility. If it is not considered plausible then the robustness of the results is supported.

8.3.2. No imputation Analysis

The primary analyses will be repeated using the observed data only, without imputations.

8.3.3. mITT analysis set Analysis

The primary analysis will be repeated using the mITT analysis set, using MI as detailed in Section 8.1.3.

8.3.4. Per Protocol Analysis

The primary analysis will be repeated using the Per Protocol analysis set, using MI as detailed in Section 8.1.3.

8.5. Secondary Effectiveness Endpoint and Analysis

Unless otherwise specified, all secondary analyses will be performed on the ITT analysis set.

8.5.1. Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MMDs to Week 12 (previous 28 days, Week 9 through Week 12)

This endpoint will be performed on the mITT analysis set, in addition to the ITT analysis set.

Define R = ((Week 12 (previous 28 days, Week 9 through Week 12) MMDs - Baseline (28-day run-in period) MMDs) / Baseline (28-day run-in period) MMD) *100

For each of the 100 complete datasets, each participant will be indicated as "responder" at week 12 if the reduction is 50% or more (i.e., $R \leq 50\%$), and "non-responder" otherwise.

The proportion of patients who have at least a 50% reduction in MMDs will be compared between the two treatment groups using the normal approximation for difference between two proportions, for each of the complete data sets. The results will be combined using Rubin's rule.

8.5.2. Change from baseline (28-day run-in period) in number of MMDs recorded over the previous 28 days at Week 4

The endpoint will be analyzed, using the 100 complete datasets, in the same manner as the primary endpoint.

The week 4 MMDs will be calculated as the number of MMDs in Days 1-28.

8.5.3. Change from baseline (28-day run-in period) in number of MMDs recorded over the previous 28 days at Week 8

The endpoint will be analyzed, using the 100 complete datasets, in the same manner as the primary endpoint.

The week 8 MMDs will be calculated as number of MMDs in the 28 days during Weeks 5-8 (Days 29-56).

8.5.4. Change from baseline (28-day run-in period) in the mean number of MMDs over 12 weeks

This endpoint will be performed on the mITT analysis set, in addition to the ITT analysis set.

The monthly number of MMDs over 12 weeks will be calculated as the average of MMDs over Weeks 1-4, MMDs at Weeks 5-8, and MMDs at Weeks 9-12, to get the average monthly MMDs. The average monthly MMDs will be used in order for the MMDs over 12 weeks to be comparable with the baseline (end of run-in period) MMDs.

The change from baseline will be calculated as the monthly number of MMDs over 12 weeks minus the baseline MMDs.

The endpoint will be analyzed, using the 100 complete datasets, in the same manner as the primary endpoint.

8.5.5. Change in the number of headaches with at least moderate severity from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12)

This endpoint will be performed on the mITT analysis set, in addition to the ITT analysis set.

Each recorded headache's severity will be scored in the following manner:

- None = 0
- Mild = 1
- Moderate = 2
- Severe = 3

Headaches that started at one period and ended in the following period will be assigned to the period in which the headache started.

The change from run-in will be calculated as (Weeks 9-12 number of headaches with at least moderate severity – run-in number of headaches with at least moderate severity).

An ANCOVA model will be used to analyze this endpoint. The dependent variable is the change in number of headaches with at least moderate severity from run-in period to Week 9-12 for each participant.

The model will adjust for the following covariates: treatment arm and number of headaches with at least moderate severity at run-in period

This analysis will use observed data only.

8.5.6. Change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score at Week 12

The MSQ is a 14-item questionnaire that is completed at baseline, Week 4, Week 8, and Week 12. Each item consists of 6 possible responses, scored 1 to 6. Higher scores represent more severe migraines.

For the purpose of calculating the MSQ total score, the responses to the 14 items will be reveres-coded (scores 1,2,3,4,5,6 will be converted to 6,5,4,3,2,1 respectively)

For each visit, the MSQ score (after reverse-coding) will be calculated as:

Total score = ([sum of the 14 reversed item scores – 14] / 70) * 100

In case of missing items, the MSQ score for the visit will be considered missing.

An ANCOVA model will be used to analyze this endpoint. The dependent variable is the change from baseline in MSQ to week 12 for each participant.

The model will adjust for the following covariates: treatment arm and baseline MSQ.

This analysis will use observed data only.

8.5.7. Change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score at Week 8

This endpoint will be analyzed in the same manner as described in Section 8.5.6, using the Week 8 assessment.

8.5.8. Change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score at Week 4

This endpoint will be analyzed in the same manner as described in Section 8.5.6, using the Week 4 assessment.

8.5.9. Change from baseline (28-day run-in period) in the Migraine Disability Assessment (MIDAS) to Week 12

The MIDAS questionnaire assesses the impact the migraine has on the participant's life. It consists of 5 questions regarding the number of days impacted. In addition, there are two questions for physician use. The endpoint will use only the first 5 questions. The MIDAS score for a visit is the sum of responses of the first 5 questions. In case of missing items, the MIDAS score for the visit will be considered missing.

This endpoint will be analyzed using Wilcoxon rank-sum test.

This analysis will use observed data only.

8.5.10. Change from baseline (28-day run-in) period to Week 12 (previous 28 days, Week 9 through Week 12) in the number of migraines with use of an acute medication

This endpoint will be performed on the mITT analysis set, in addition to the ITT analysis set.

The number of migraines with use of an acute medication will be counted for the run-in period and for post randomization period.

The change from baseline will be calculated as number of migraines in weeks 9-12 minus number of migraines in the run-in period with use of an acute medication.

Migraines that started at one period and ended in the following period will be assigned to the period in which the migraine started.

An Analysis of Covariance (ANCOVA) model will be used to analyse this endpoint. The dependent variable is the change from baseline to Week 12 in the number of migraines with use of an acute medication each participant.

The model will adjust for the following covariates: treatment arm, baseline number of migraines with use of an acute medication. The analysis will use only observed data.

8.5.11. Change in the number of MHDs from baseline (28-day run-in) to Week 12 (previous 28 days, week 9 through Week 12)

This endpoint will be calculated and analyzed as described in Section 8.1.3, using MHDs instead of MMDs.

This endpoint will be performed on the mITT analysis set, in addition to the ITT analysis set.

8.6. Multiplicity Control

No multiplicity adjustment will be made to secondary endpoints, sensitivity analyses, and subgroups. *P*-value and confidence interval for secondary endpoints not controlled for multiplicity and exploratory endpoints will be nominal and will not be used for statistical inference.

8.7. Exploratory Endpoints

All exploratory analyses will be conducted on the ITT analysis set.

[redacted]

[redacted]

[redacted]

8.7.13. Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MHDs at Week 12 (previous 28 days, Week 9 through Week 12)

This endpoint will be calculated and analyzed as described in Section 8.5.1, using MHDs instead of MMDs.

8.7.14. Change from baseline (28-day run-in period) in the mean number of MHDs over 12 weeks.

This endpoint will be calculated and analyzed as described in Section 8.5.4, using MHDs instead of MMDs.

8.7.15. Change from baseline (28-day run-in period) in the number of MHDs recorded over the previous 28 days at Week 4

This endpoint will be calculated and analyzed as described in Section 8.5.2, using MHDs instead of MMDs.

8.7.16. Change from baseline (28-day run-in) in the number of MHDs recorded over the previous 28 days at Week 8

This endpoint will be calculated and analyzed as described in Section 8.5.3, using MHDs instead of MMDs.

8.8. Patient Global Impression of Change (PGI-C) score at Week 12

The Patient Global Impression of Change (PGI-C) is a self-reported, 7-point scale depicting a patient's rating of overall improvement.

The PGI-C will be measured at Week 12.

T-test will be used to analyze this endpoint.

8.8.1. Shift from High Frequency Episodic Migraine (HFEM) at baseline (28-day run-in period) to Very Low Frequency Episodic Migraine (VLFEM) or Low Frequency Episodic Migraine (LFEM) at Week 12 (previous 28 days, Week 9 through Week 12)

During the 28-day run-in period each participant will be classified as having High Frequency Episodic Migraine (HFEM; 8-14 MMDs) or Low Frequency Episodic Migraine (LFEM; 4-7 MMDs).

During weeks 9-12, participants will be classified as HFEM, LFEM or Very Low Frequency Episodic Migraine (VLFEM; < 4 MMDs). Note that per inclusion criteria at baseline there are no VLFEM participants.

A shift table will be presented including the number and percentage of participants shifting from each category at run-in period to each category at Weeks 9-12, by treatment group.

This analysis will include only subjects with at least 10 days of reporting during Week 9-12, and number of migraines will be prorated as described in Section 6.3. Patients with less than 10 days of reports will be considered missing in this analysis.

9. SAFETY ANALYSIS

All safety analyses will be conducted on the safety analysis set and will be descriptive.

AE will be recorded from date of signing the ICF and onwards. All AEs will be coded by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.

Summaries will present non-treatment emergent AEs (AEs started before first day of treatment) and treatment-emergent AEs (TEAE; AEs started after first day of treatment) separately.

In an overview table, the number and percentage of participants who experienced a TEAE, non-TEAE, serious TEAE, treatment related TEAE, died due to an AE, or discontinued from study treatment due to a TEAE will be summarized by treatment.

The percentages of participants with TEAEs will be summarized by treatment using MedDRA preferred term nested within system organ class (SOC). Events will be ordered by decreasing frequency within SOC, and SOC with be ordered by decreasing frequency.

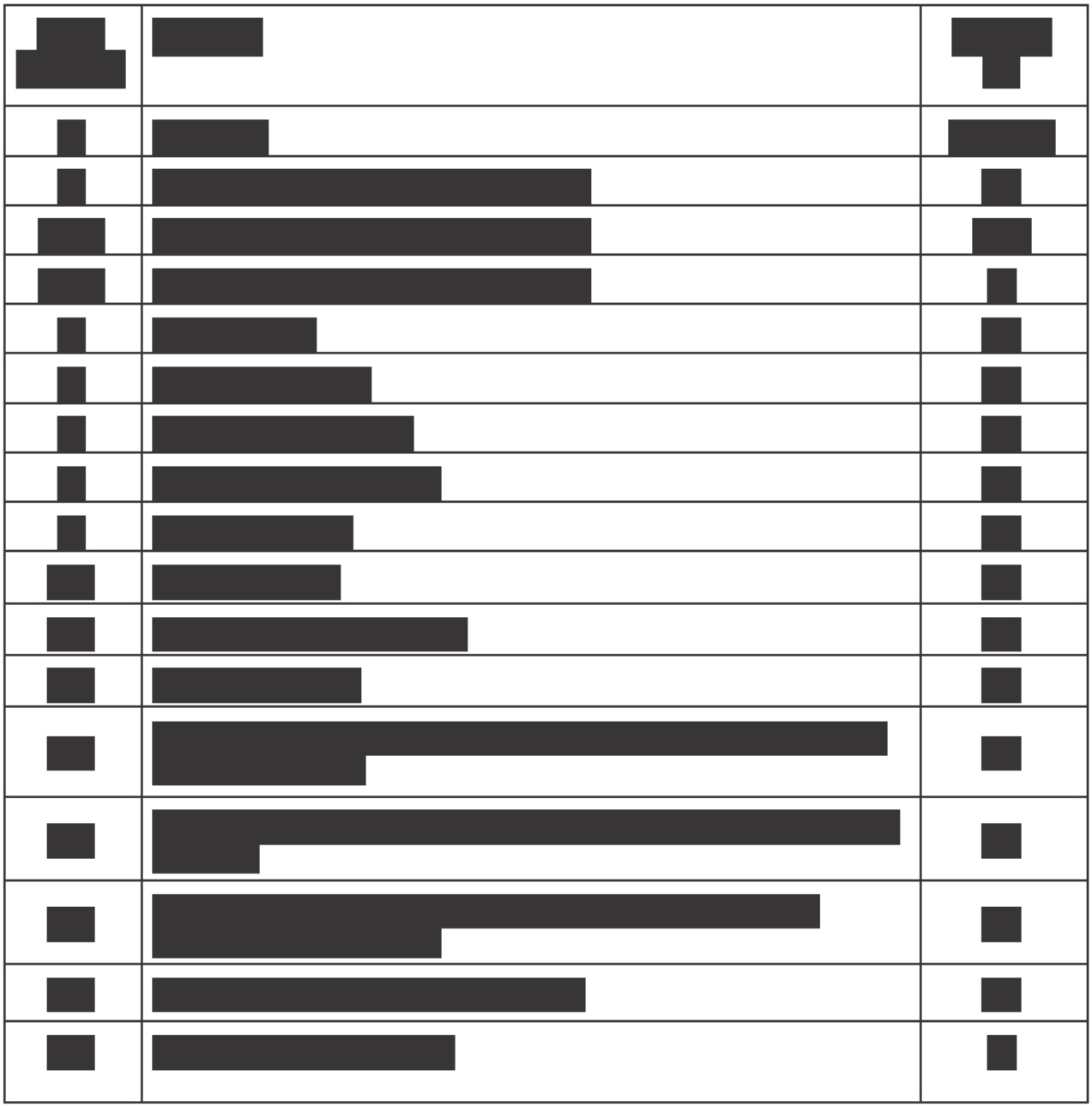
Similar summary will be presented for non-TEAE, serious TEAE, treatment related TEAE and TEAE related to worsening of migraine.

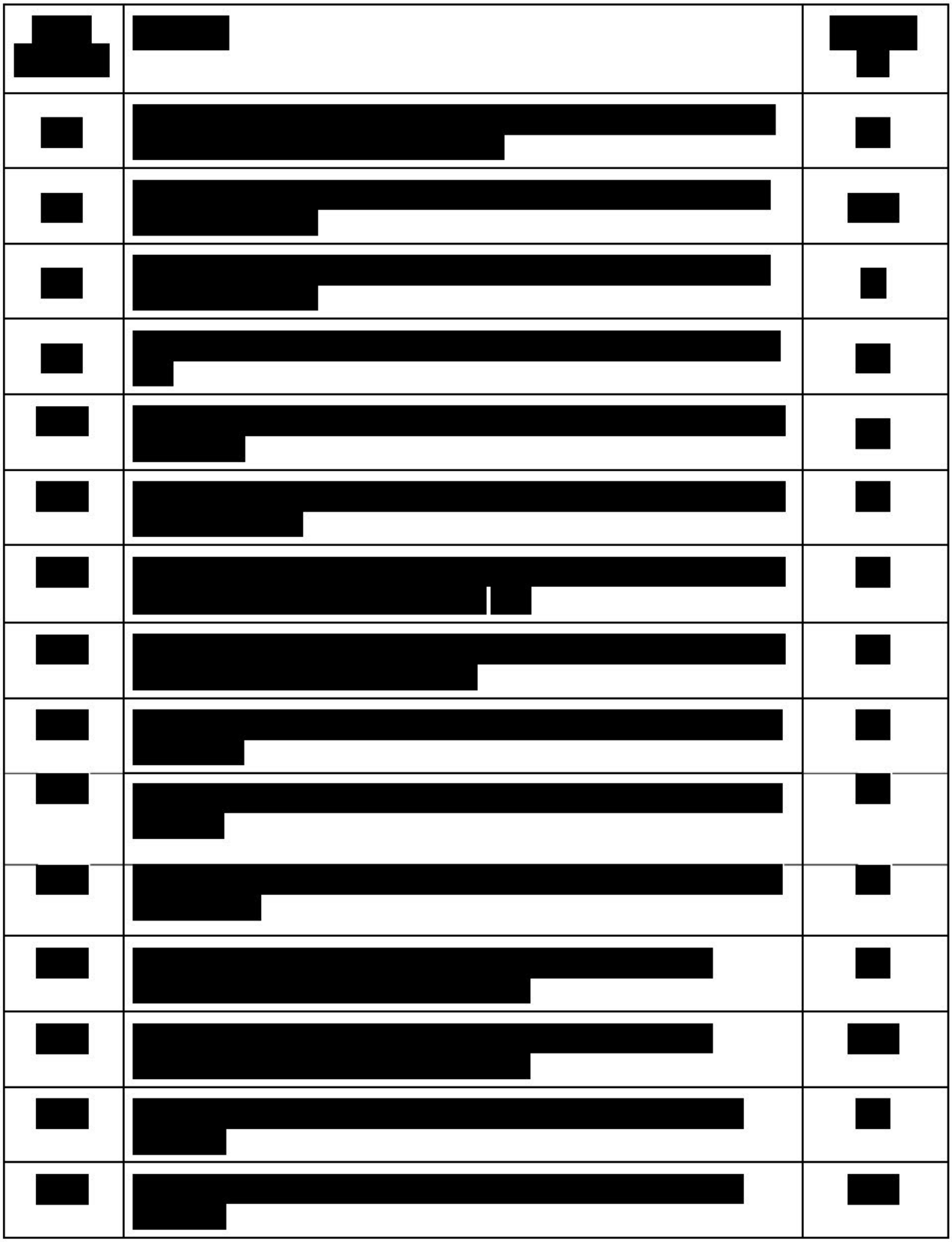
AEs with missing start date will be considered as a TEAE.

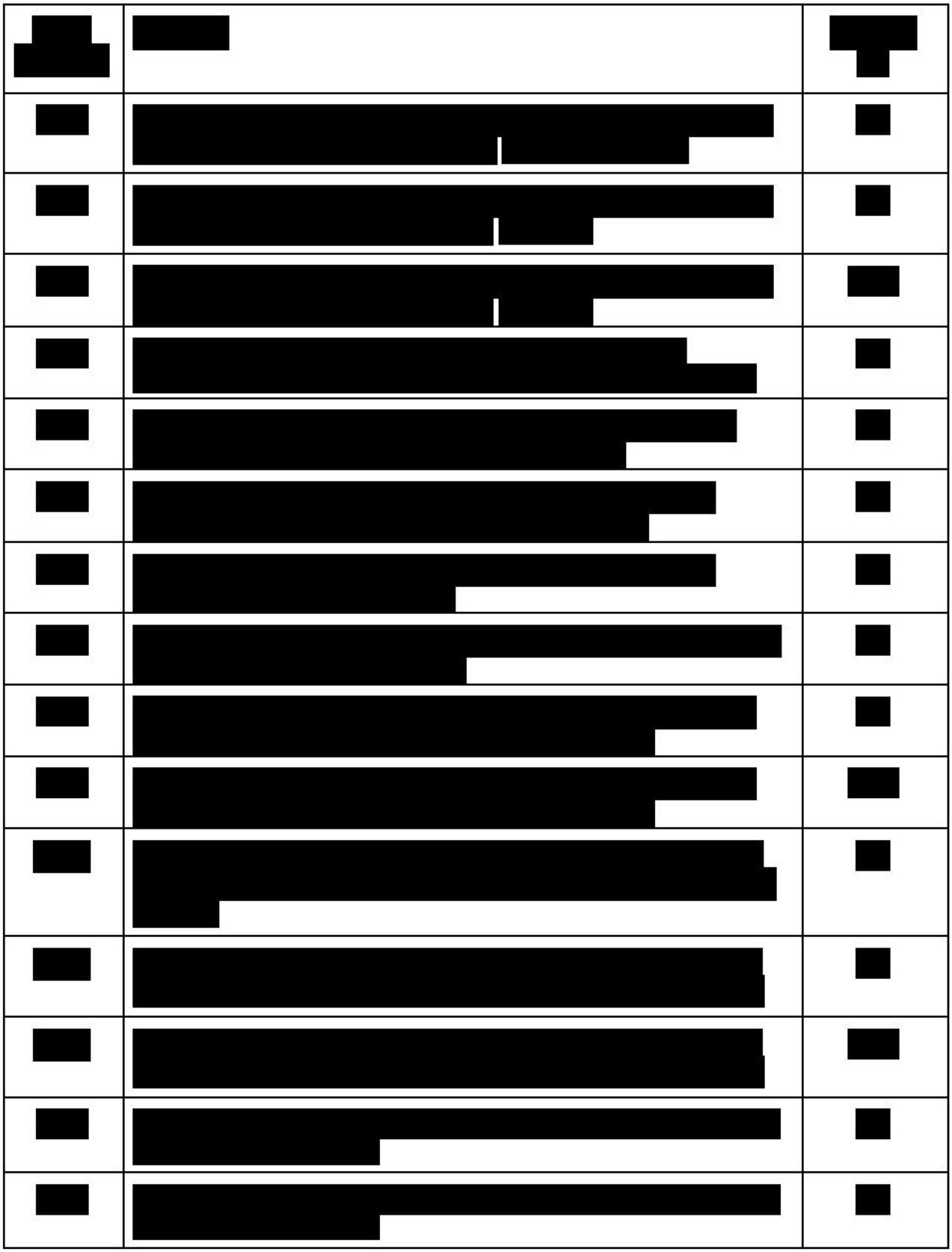
10. TABLE OF CONTENTS

10.1. Tables

Tables will typically include a summary of assessments per visit, change from baseline, and difference between CT-132 and the digital control. Confidence intervals for change from baseline and difference between groups, and *p*-values for comparison between treatment groups will be included when statistical model is utilized. Tables will be numbered sequentially. Table headers will include the name of the endpoint and type of analysis.







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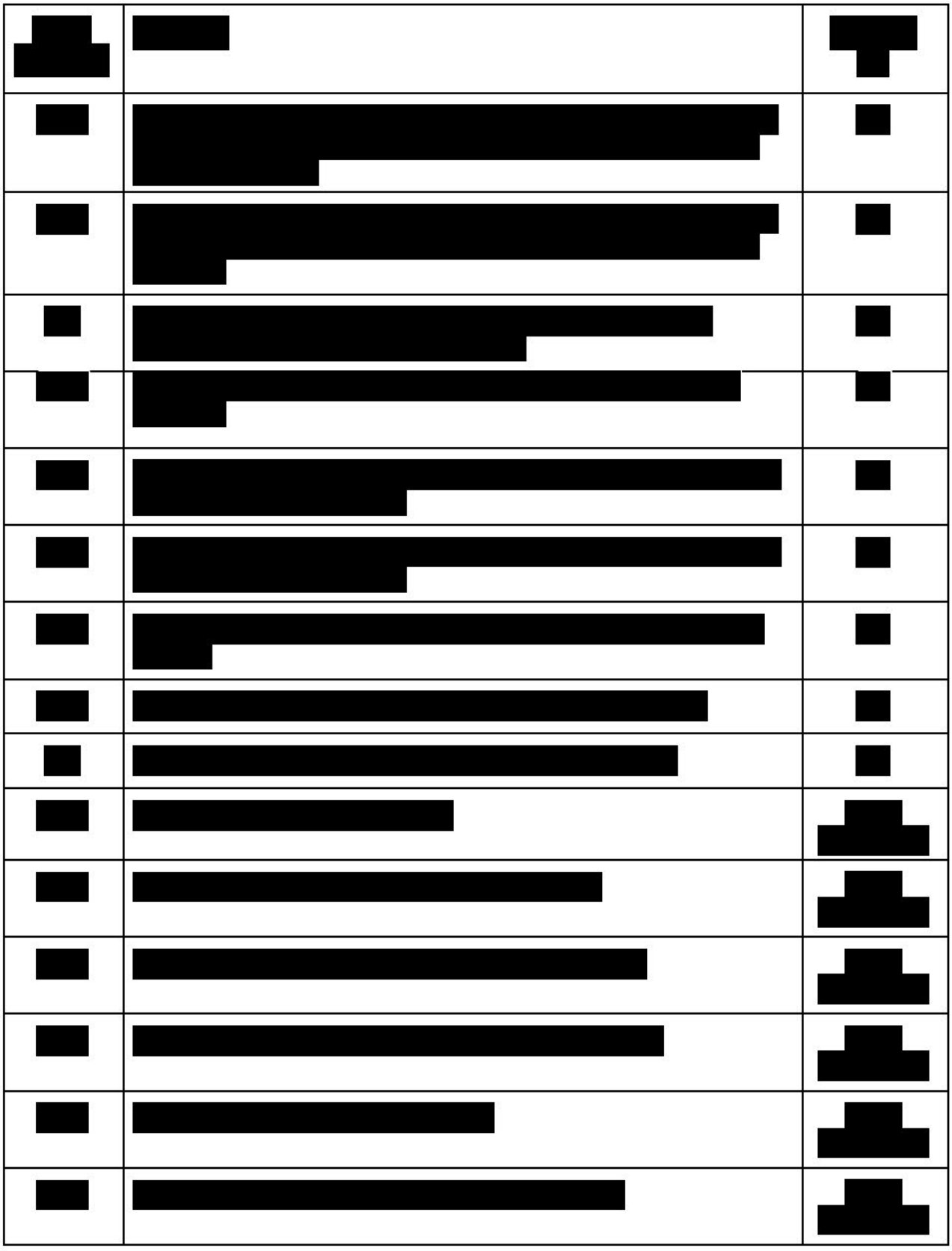

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10.2. Figures

Figures will be numbered in a similar manner to the tables.

[redacted]

10.3. Listings

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11. APPENDIX

11.1. Appendix A - [redacted]