16.1.9 Documentation of statistical methods

The following documents are included:

[redacted]

Analysis of proportions

The Cochran-Mantel-Haenszel (CMH) test, incorporating prior anti-tumor necrosis factor use as a stratification factor, was used to compare response rates of response–type variables between [redacted] tildrakizumab and placebo. In addition, the Mantel-Haenszel common risk (the response rate) difference between [redacted] tildrakizumab and placebo and the [redacted] confidence interval (CI) were estimated. Should assumption per the Mantel-Fleiss criterion not be satisfied, the comparison was to be based on a Fisher's exact test after collapsing across levels of the stratification factor. In this case, the response rate difference and CI was based on a normal approximation without considering stratification.

The primary efficacy variable is ASAS20 at [redacted] ASAS20 was analyzed with CMH test as described above. Early withdrawals and any subjects with ASAS20 undeterminable at [redacted] were classified as non-responders. Subjects who failed to show minimal response to treatment (defined as [redacted] improvement from Baseline in total back pain or inflammation) at [redacted] may have had their background medications adjusted according to the maximum permitted daily dose described in the protocol and continued in the study. Any subject requiring these adjustments was counted as a non-responder for the primary analysis.

The sample SAS codes are:

[redacted]

The secondary and exploratory response-type endpoints (ASAS[redacted], ASAS[redacted], ASAS[redacted] etc.) were analyzed similarly.

Mixed model repeated measures analysis of continuous endpoints

A mixed model repeated measure (MMRM) analysis was performed. The SAS procedure PROC MIXED was used. The preferred model included the fixed categorical effects of treatment, visit, treatment-by-visit interaction, and prior TNF use (yes/no), as well as the continuous fixed covariate of baseline value. An unstructured matrix for the within-subject error variance-covariance was used. The denominator (degrees of freedom) was calculated according to the Kenward-Roger method.

In case of non-convergence with the unstructured matrix, other within-subject error variance-covariance matrices, such as compound symmetry (CS), was considered.

The model provided least-squares mean estimates, standard errors, [redacted] CIs and [redacted] p-values for mean change at all time points between treatments (tildrakizumab vs. placebo).

Continuous endpoints (change from baseline in PtGA of disease activity, Total Back Pain, Nocturnal Pain, Inflammation, BASFI, BASMI, BASDAI, ASQoL, ASDAS-CRP, ASDAS-ESR, MASES, SF-36, FACIT-fatigue, TJC46, SJC44, hsCRP, SPARCC MRI Index of Disease Activity Score of the SI Joints, SPARCC MRI Index of Disease Activity Score of the Spine, and Modified Berlin ASspiMRI) up to [redacted] analyzed based on a MMRM analysis that includes the fixed effects of treatment, visit, treatment by visit interaction, prior anti-TNF use (yes/no), and Baseline value. Due to placebo group switching to [redacted] tildrakizumab at [redacted], the comparison between active drug and placebo was not performed for the endpoints collected after [redacted].

Below is an example of the SAS code for the MMRM:

[redacted]

[redacted]

Statistical Analysis Plan (SAP)

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Phase 2a Study to Evaluate the Efficacy and Safety of Tildrakizumab in Subjects with Active Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis
Protocol Number:	CLR_16_22
Protocol Version, Date	V3.0 Final, 19 Mar 2018
[redacted]	[redacted]
Document Version, Date:	Final v2.0, 01 Oct 2019

Prepared by:

[redacted]

Confidentiality statement:

- The information provided in this document is strictly confidential.
- The Recipients of the SAP must not disclose the confidential document and any related information to other persons.
- In addition, they must keep this confidential document in a controlled environment which prevents unauthorized access to the document.

[redacted]

SIGNATURE PAGE

[redacted]

[redacted]

Approved at Sun Pharma Advanced Research Company Ltd by:

Rocco Ballerini

Rocco Ballerini 08 Oct 2019 20:21:022+0000

REASON: I approve this document

4527a681-b6fb-4e53-bc97-98fb389dd032

Rocco Ballerini, Associate Vice President- Biostatistics and Data Management

Date

[redacted]

Statistical Analysis Plan (SAP)

REVISION HISTORY

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

Abbreviation or special term	Explanation
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI	Ankylosing Spondylitis Spine Magnetic Resonance Imaging Activity Score
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	Body Mass Index
CI	Confidence Interval
cm	Centimeter
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
DBL	Database Lock
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
FACIT	Functional Assessment of Chronic Illness Therapy

FAS	Full Analysis Set
ESR	Erythrocyte Sedimentation Rate
hsCRP	high sensitivity C-reactive protein
IA	Interim Analysis
IMP	Investigational Medicinal Product
IVRS	Interactive Voice Response System
kg	Kilogram
MACE	Major Adverse Cardiac Events
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurements
MRI	Magnetic Resonance Imaging
n	Number of non-missing observations
nr-axSpA	non-radiographic axial Spondyloarthritis
PGA	Physician Global Assessment
PK	Pharmacokinetics
PPAS	Per Protocol Analysis Set
PT	Preferred Term
PtGA	Patient Global Assessment
Q1	Lower Quartile
Q3	Upper Quartile
q4wk	Every 4 weeks
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36	36-item Short Form
SI	Standard International
SJC44	swollen joint count of 44 joints
SOC	System Organ Class
SOP	Standard Operating Procedure
SPARCC	SpondyloArthritis Research Consortium of Canada

$T_{1/2}$	Half-life
TEAE	Treatment Emergent Adverse Event
TJC46	tender joint count of 46 joints
TLFs	Tables, Listings and Figures
T_{max}	Time of maximal concentration
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
VAS	Visual Analog Scale

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed description of the statistical methods, data derivations and data presentations to be employed for study protocol CLR_16_22 "A Randomized, Double-Blind, Placebo-Controlled Phase 2a Study to Evaluate the Efficacy and Safety of Tildrakizumab in Subjects with Active Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis" which was originally issued on [redacted] and amended on [redacted] and [redacted].

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

This SAP supersedes the statistical considerations identified in Protocol CLR_16_22 and where considerations are substantially different, they will be identified as such in this document.

This SAP has been developed and approved prior to database lock and unblinding of the clinical database for Protocol CLR_16_22.

2 STUDY OBJECTIVES

2.1 Primary objectives

Part 1

- To evaluate the efficacy of tildrakizumab in subjects with ankylosing spondylitis (AS) or non-radiographic axial spondyloarthritis (nr-axSpA), as measured by the proportion of subjects achieving Assessment of SpondyloArthritis international Society (ASAS) [redacted] response criteria at [redacted]

Parts 1 and 2

- To assess the safety/tolerability and immunogenicity of tildrakizumab in subjects with AS or nr-axSpA.

2.2 Secondary objectives

Parts 1 and 2

- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects achieving ASAS20 response criteria at [redacted], and ASAS40 response criteria at [redacted], and proportion of subjects who require adjustment of background therapy.
- To characterize the pharmacokinetics (PK) of tildrakizumab in subjects with AS or nr-axSpA.

2.3 Exploratory objectives

Parts 1 and 2

- To evaluate the efficacy of tildrakizumab in subjects with AS or Nr-axSpA, as measured by the proportion of subjects who achieve ASAS20 or ASAS40 at other measured time points.
- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects who achieve ASAS70 or ASAS5/6.
- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the change from Baseline in ASAS components, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life questionnaire (ASQoL), Visual Analog Scale (VAS) (total back pain and nocturnal pain score), Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP), ASDAS erythrocyte sedimentation rate (ESR), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), short form 36 (SF-36), Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue,

high-sensitivity CRP (hs)CRP, SpondyloArthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) Index of Disease Activity of the Sacroiliac (SI) Joints, SPARCC MRI Index of Disease Activity of the Spine, and Modified Berlin Ankylosing Spondylitis Spine Magnetic Resonance Imaging Activity Score (ASspiMRI), swollen joint count of 44 joints (SJC44), and tender joint count of 46 joints (TJC46) at measured time points.

- To evaluate the tildrakizumab exposure/response relationship.

Part 3

- To assess the effect of investigational medicinal product (IMP) discontinuation on ASAS20, ASAS40, ASAS70, ASAS5/6, ASAS components, BASDAI, BASMI, BASFI, VAS (total back pain and nocturnal pain score), MASES, SF-36, FACIT-fatigue, TJC46, and SJC44 at measured time points.
- To evaluate immunogenicity following IMP discontinuation.
- To characterize the PK of tildrakizumab in subjects with AS or nr-axSpA following IMP discontinuation.

3 STUDY DESIGN

3.1 General study design

This is a randomized, multinational, double-blind, placebo-controlled, Phase 2a study. The study will consist of a Screening Period [redacted] Part 1, a double-blind, placebo-controlled period [redacted] Part 2, a [redacted] follow-up period [redacted] and Part 3, a [redacted] During the wash-out period, subjects will no longer receive tildrakizumab and will be treated according to the Investigators' discretion.

At least [redacted] subjects with active AS (Stage 1 of study) and 90 subjects with active nr-axSpA (Stage 2 of study) who satisfy the inclusion criteria and do not meet the exclusion criteria will be enrolled in this study. Approximately [redacted] subjects will be randomized into the Double-Blind treatment period.

The Study Flow Chart is presented in Figure 1.

Figure 1: Study Flow Chart

[redacted]

Abbreviations: AS = ankylosing spondylitis; mg = milligram;
nr-axSpA = non-radiographic axial spondyloarthritis; Wk = week

Subjects who fail to show minimal response to treatment (defined as [redacted] from Baseline in pain [assessed by total back pain VAS [redacted]] or inflammation [assessed using the last[redacted] stiffness assessments in the BASDAI]) at [redacted] in both stages of the study may have their background medications adjusted according to the maximum permitted daily dose and continue in the study.

Tildrakizumab subjects in both stages who achieve ASAS20 at [redacted] will receive treatment with [redacted] tildrakizumab [redacted] until [redacted] Subjects receiving tildrakizumab during Part 1 who do not achieve ASAS20 at [redacted] will discontinue IMP treatment and enter the [redacted] washout period. Subjects randomized to receive placebo during Part 1 of both stages of the study who complete the [redacted] visit will continue to Part 2 and receive tildrakizumab 200 mg q4 weeks until [redacted] even if they do not achieve ASAS20. Subjects discontinued from IMP at any time (apart from withdrawal of informed consent) will be required to complete the EoT [redacted] assessment a minimum of [redacted] after the last dose of IMP and enter the [redacted] washout period. Subjects who withdraw from the study during Part 3 will undergo the [redacted] (End of Study [EoS]) assessments at least 4 weeks after their last visit.

On completion of Part 2, subjects may enter the long-term extension (LTE) study, [redacted], providing they meet the inclusion/exclusion criteria for the LTE study and the Investigator deems they would benefit from continued treatment with tildrakizumab. In circumstances where the LTE study site activation has not occurred at the time the subject reaches the end of Part 2, they may enter from washout period if the required eligibility conditions are met.

3.2 Randomization and blinding

3.2.1 Randomization

A randomization schedule will be computer-generated before the start of the study. After all screening procedures are performed and results of screening tests are available (i.e., between the Screening visit and [redacted]), [redacted] will be activated in the interactive voice recognition system (IVRS), and assigned randomly on a [redacted] basis to the following treatment groups for cohorts of [redacted], respectively:

- A: [redacted] tildrakizumab, [redacted]
- B: Placebo, administered by [redacted]

Randomization will be performed by the [redacted]. Subjects will be stratified by prior anti-tumor-necrosis factor (anti-TNF) use (yes/no). Subjects with prior anti-TNF use will be capped [redacted] of the total number of subjects.

[redacted] (Stage 1) subjects will begin upon study approval; recruitment for [redacted] (Stage 2) subjects will begin only upon written notification by the Sponsor to the Competent Authorities and Investigators.

3.2.2 Blinding

This is a double-blind study. None of the study team, the subject, and the Sponsor (or representative) will be aware of the administered study drug to each subject until the completion of their double-blind treatment ([redacted] visit) and wash-out period. A separate document will provide further details related to unblinding of personnel involved in reporting activities for the Interim Analysis (IA).

PK and anti-drug antibodies (ADA) data will be kept confidential only after database lock and unblinding at study completion.

3.2.3 Unblinding

In an emergency, in which the Investigator must know a subject's treatment allocation to ensure the subject's safety, the Investigator will contact IVRS. When the Investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The Investigator will then receive details of the IMP for the specified subject. The system will automatically inform the ICON Site Monitor, the medical monitor, and the [redacted] Project Manager that the code has been broken, but no treatment assignment will be communicated.

3.3 Study treatments and assessments

The maximum study duration from screening to end of the wash-out period is [redacted].

All subjects eligible for study participation will enter the double blind treatment period and receive one of the 2 treatments assigned per the schedule outlined in the study flow chart. Study drug will be supplied as pre-filled syringes and a subject at a visit is expected to receive two syringes packed in a kit. Below are the details:

- [redacted]: subjects will receive tildrakizumab [redacted] ([redacted] of [redacted]) at [redacted].
- Placebo arm, [redacted] will be administered at [redacted] and [redacted] Subjects will then receive tildrakizumab [redacted] at [redacted].

If a subject misses a visit and/or a scheduled dose of IMP, the site must reschedule a visit to ensure the dose of IMP is taken as soon as possible within the visit window. If after 2 attempts to reschedule, the subject still is not able to take the dose, the Sponsor should be contacted to

determine if the subject should be discontinued from the study.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Schedule of Assessments in [redacted] below.

Table 2: Schedule of Assessments (Part 1 and 2)

[redacted]

[redacted]

[redacted]

[redacted]

Statistical Analysis Plan (SAP)

[redacted]

[redacted]

[redacted]

Statistical Analysis Plan (SAP)

[redacted]

[redacted]

Table 2: Schedule of Assessments (Part 3)

[redacted]

[redacted]

Statistical Analysis Plan (SAP)

[redacted]

[redacted]

4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint

The primary efficacy endpoint is the proportion of subjects who achieve ASAS20 at [redacted]

ASAS20 response is defined as an improvement of [redacted]

The components of the ASAS[redacted] assessments that will be used in this study are:

- PtGA of disease activity (VAS in mm)
- Total Back Pain (VAS in mm)
- BASFI (VAS in mm)
- Inflammation [average score of questions 5 and 6 of BASDAI] (VAS in mm)

For the details on BASFI derivation, see [redacted] for the related endpoint. For inflammation, if either [redacted] of BASDAI is missing, non-missing score will be used. If both [redacted] are missing, then Inflammation is set to missing.

For any component which is not on a scale of [redacted], they will be converted to 0 to 100 before calculating ASAS.

If the value in any of the components at a time point is missing, the component variables that are not missing will be used to determine the response status. As a general principle, if there are sufficient non-missing components to determine whether the ASAS endpoint is a response or non-response, then ASAS endpoint is not missing, else if the available non-missing components are not sufficient to determine the response status of ASAS endpoint then it is considered missing.

If the baseline value of any component is [redacted] the following algorithm will be used in evaluating the percent change from baseline:

- If change from baseline is also equal to 0, then percent change from baseline is set to be [redacted];
- If change from baseline is [redacted] then percent change from baseline is set to be [redacted]

These percentages will be used to derive the ASAS endpoints.

4.2 Secondary efficacy endpoints (up to [redacted])

The secondary efficacy endpoints of this study are:

Parts 1 and 2

- The proportion of subjects who achieve ASAS20 at [redacted]
- The proportion of subjects who achieve ASAS40 at [redacted]

  [redacted]
- The proportion of subjects who require adjustment of background therapy

4.3 Exploratory endpoints

The exploratory endpoints of this study are:

Parts 1 and 2:

- The proportion of subjects who achieve ASAS20 or ASAS40 at other measured time points
- The proportion of subjects who achieve ASAS70 at measured time points

  ASAS70 will be derived similarly as for ASAS40 by using [redacted] and [redacted]. i.e. ASAS70 response is defined as an improvement of [redacted] absolute improvement of [redacted] units from Baseline in a VAS for at [redacted] domains: PtGA; Total Back Pain; BASFI; and Inflammation. No worsening of [redacted] VAS on a [redacted] scale in the remaining [redacted] domain.
- The proportion of subjects who achieve a ASAS5/6 response at measured time points

  ASAS5/6 response is defined as a [redacted]s (physical function [BASFI], Total Back Pain, PtGA of disease activity, Inflammation [mean of [redacted] of the BASDAI], spinal mobility [BASMI], and acute phase reactants [CRP]).
- Change from Baseline in ASAS components at measured time points
- Change from Baseline in BASDAI at measured time points

  BASDAI is derived by computing the mean score of the [redacted]) and then adding that value to the sum of the score for the [redacted] and then [redacted] It may be written as:

  [redacted]

  In the case of any single missing question, the BASDAI will be calculated using the remaining [redacted]. Specifically, if [redacted] is missing,

[redacted] If more [redacted].

BASDAI score ranges from [redacted].

- Change from Baseline in BASMI at measured time points

  BASMI is a combined index to assess spinal mobility. BASMI score is collected on the CRF page and ranges [redacted]

- Change from Baseline in BASFI at measured time points

  BASFI is derived by computing the mean of the score for the 10 questions. BASFI can be calculated with up to 3 missing items by adjusting the denominator for the number of non-missing items. If more than 3 items are missing, BASFI should be set to missing.

  [redacted]

- Change from Baseline in ASQoL at measured time points

  ASQoL total score is calculated by summing the [redacted] and ranges [redacted]. Cases with more than three missing items (ie more than [redacted]) cannot be allocated a total score. For cases with between one and three missing items, the total score is calculated as follows: [redacted] for the items affirmed and [redacted]

- Change from Baseline in VAS (total back pain and nocturnal pain score) at measured time points

- Change from Baseline in ASDAS-CRP and ASDAS-ESR at measured time points

  [redacted]

  Note: Back Pain is from BASDAI [redacted]); Duration of Morning Stiffness is from BASDAI [redacted] Peripheral Pain/Swelling is from BASDAI [redacted]); Patient Global is from PtGA of disease activity [redacted]); CRP - the natural logarithm of CRP in mg/L; ESR- the square root of ESR in mm/h.

- Change from Baseline in MASES at measured time points

  MASES score is recorded in the CRF and ranges [redacted].

- Change from Baseline in SF-36 at measured time points [redacted]

- Change from Baseline in FACIT-fatigue at measured time points

  FACIT-fatigue is a [redacted] item questionnaire with each item score ranges from [redacted] FACIT-fatigue total score ([redacted]) is calculated by summing the [redacted] items with [redacted] being reversed [redacted]) prior to summing.

  In case of some answers are missing, the total score is prorated from the score of the answered items as long as more than 50% of the items are answered. ie, FACIT-fatigue = 13*mean(non-missing of Q1 to Q13).

- Change from Baseline in TJC46 and SJC44 at measured time points
- Change from Baseline in hsCRP serum levels at measured time points
- Change From Baseline in SPARCC MRI Index of Disease Activity Score of the SI Joints at measured time points
- Change From Baseline in SPARCC MRI Index of Disease Activity Score of the Spine at measured time points
- Change From Baseline in Modified Berlin ASspiMRI at measured time points

Part 3:

ASAS20, ASAS40, ASAS70, ASAS5/6, ASAS components, BASDAI, BASMI, BASFI, SF-36, VAS (total back pain and nocturnal pain score), MASES, FACIT-fatigue, TJC46, and SJC44 at measured time points.

4.4 Safety endpoints

The safety endpoints of this study are:

- Adverse events (AEs)
- Laboratory assessments
- Suicidal ideation and behavior (C-SSRS)
- Vital signs
- ECG
- Physical examination
- ADA to tildrakizumab, including titer and neutralizing antibodies

5 SAMPLE SIZE AND POWER

In each subject cohort (AS and nr-axSpA), approximately 45 subjects will be randomized per arm in a 1:1 ratio to tildrakizumab 200 mg or placebo and will be stratified by anti-TNF use (yes/no). This sample size achieves 80% power (accounting for futility assessment) to detect a treatment effect in ASAS20 at [redacted] (placebo ASAS20 = [redacted]; tildrakizumab ASAS20 = [redacted]). The test statistic used is the [redacted] Cochran-Mantel-Haenszel (CMH) test at the [redacted] significance level. A [redacted] drop-out rate has been assumed.

6 ANALYSIS POPULATIONS

6.1 Full Analysis Set (FAS)

The FAS will include all randomized subjects who have received at least 1 dose of IMP (tildrakizumab or placebo). Analyses will be based on randomized treatment.

6.2 Per Protocol Analysis Set (PPAS)

The PPAS will include all subjects in the FAS without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variables. The deviations may include but are not limited to:

- Key inclusion/exclusion criteria not satisfied
- Presence of relevant protocol deviations with respect to factors likely to affect the efficacy of treatment where the nature of protocol deviation will be defined before breaking the blind
- Rescue medication use
- Inadequate study medication compliance which will be determined before breaking the blind

Major protocol deviations to be excluded from the PPAS will be finalized and documented in a memo prior to the lock and unblinding of the database.

6.3 Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who received at least 1 dose of IMP. Analyses will be based on the actual treatment received.

6.4 PK Analysis Set

The PK Analysis Set will include all subjects in the Safety Analysis Set who have sufficient tildrakizumab concentration data to obtain reliable estimates of at least one PK parameters.

6.5 ADA Evaluable Set

The ADA Evaluable Set will include all subjects in the Safety Analysis Set who have at least 1 ADA data point after the date of first IMP administration. Assay results from the placebo portion of the trial will not be included in the immunogenicity assessment, although subjects who are randomized to placebo in Part 1 will be included in the assessment if they are treated with tildrakizumab in Part 2.

6.6 Protocol deviations/violations and exclusions from analysis sets

All deviations and exclusions of subjects from analysis sets will be identified at the Classification

Meeting just prior to study unblinding, through clinical review input provided by Sponsor, using the following sources of information:

- Supportive subject listings, provided by the [redacted] lead statistician ahead of the Classification Meeting, based on data recorded on the eCRF.
- Protocol Deviation Logs, provided by [redacted] Medical/Clinical.

Further, deviations from the protocol will be classified as major/minor or key/non-key depending on documentation in [redacted]

The protocol deviations that will lead to subject exclusion from the PPAS are listed as below. It is possible that unexpected deviations will arise as the study moves forward. Therefore, more deviations may be added to the list later. Prior to database lock, a classification meeting will be conducted to identify subjects to be excluded from PPAS, and the decision will be documented in a separate file.

- Subject with BASDAI [redacted] at Screening or Response to the BASDAI question 'How would you describe the overall level of AS neck, back or hip pain you have had?' of [redacted] on the VAS [redacted] at Screening
- Non-compliance with study treatment [redacted])
- Disallowed concomitant medications
- Treatment error - at least one dose of randomized treatment and one dose of incorrect treatment were administered to a subject.

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived Variables

Details for deriving efficacy variables are discussed in [redacted]. The below set of variables are the basic demographic variables and some general variables.

Variables	Formula
Body mass index (BMI; kg/m2)	weight (kg)/[height (m)]2
Study day at any visit	(visit date – date of first IMP administration) + 1 for visit dates on or after first IMP dosing date; (visit date – date of first IMP administration) for visit dates before first IMP dosing date
Change from baseline	[redacted]
Percent change from baseline	[redacted]

7.2 Handling of missing data and outliers

7.2.1 Missing data analysis methods

In the primary analysis, ASAS20 response rate at [redacted], missing values will be handled by setting the ASAS20 value to nonresponsive. This approach will be used for all "response-type" endpoints (ASAS40, ASAS70, and ASAS5/6) at all time points.

For a composite "response-type" endpoint (such as ASAS[redacted]), if values in any of the components at a time point are missing, the component variables that are not missing will be used to determine the response status. If one cannot determine the response status in the presence of missing components, then the composite response-type endpoint status is considered "non-response" for that time point.

For the BASDAI, BASMI, BASFI, MASES, SF-36, and FACIT instruments, rules suggested by the developers of these will be followed in calculating scores when individual question/items may be missing.

Details on handling missing data are outlined in [redacted].

In general, missing values in any of the endpoints will not be imputed when summarizing these endpoints using descriptive statistics.

In addition, missing values for safety endpoints will not be imputed.

7.2.2 Handling of missing or incomplete dates

Imputation rules for missing or partial AE start date are defined below:

If the start date has month and year but day is missing, the first day of the month will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the start date has year, but day and month are missing, the 1st of January will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the start date of an event is completely missing, then it is imputed with the first dose date.

Imputation rules for missing or partial AE stop date are defined below:

- If the stop date has month and year but day is missing, the last day of the month will be imputed
- If the stop date has year, but day and month are missing, the 31th of December will be imputed

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

Imputation rules for missing or partial medication start/stop dates are defined below:

Missing or partial medication start date:

- If only Day is missing, use the first day of the month.
- If Day and Month are both missing, use the first day of the year.

Missing or partial medication stop date:

- If only Day is missing, use the last day of the month.
- If Day and Month are both missing, use the last day of the year.
- If Day, Month and year are all missing, assign 'continuing' status to stop date

8 STATISTICAL METHODS

8.1 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of [redacted]

Summaries for AS or nr-axSpA will be presented separately. Summary statistics will also be presented by treatment group. Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum and maximum. One additional decimal point for mean and median and 2 additional decimal points for SD will be used.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

Two-sided 95% confidence intervals (CI) will be provided when relevant.

For summary purposes, baseline will be defined as the last available value prior to the date of first IMP administration; all summaries will be presented by treatment group, unless otherwise specified.

For reporting purpose, summary tables for efficacy variables and safety variables will be displayed by nominal visit as appropriate. Unscheduled assessments will not be included in the summary tables, but will be displayed in data listings.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by cohort, treatment group, subject number, date/time and visit. The treatment group as well as patient's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all randomized subjects.

The treatment groups will be displayed in the format below in tables including Part 1 only:

- [redacted] Tildrakizumab
- Placebo

The treatment groups will be displayed in the format below for tables including Parts 2 and/or 3 and all listings:

- [redacted] Tildrakizumab
- Placebo → [redacted] Tildrakizumab

8.2 Protocol deviations

Population membership details will be listed, including reason for exclusion from each population.

All major protocol deviations identified will be summarized by treatment group and overall.

A listing will include the inclusion/exclusion criteria violated at Screening and at Baseline Visits as well as other protocol deviations identified based on data recorded on the eCRF and/or protocol deviation Logs from ICON Medical.

8.3 Subject disposition

The number of subjects in the following categories will be summarized overall and by treatment group:

- Randomized
- Full Analysis Set (FAS)
- Per Protocol Analysis Set (PPAS)
- Safety Analysis Set

The number and percentage (based on FAS) of subjects in each of the following disposition categories will be summarized overall and by treatment group:

- Completed treatment at Parts 1 and 2
- Prematurely discontinued the treatment and the reasons for discontinuation
- Completed study (i.e., completed the wash-out period)
- Prematurely discontinued the study and the reason for discontinuation

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation.

8.4 Demographics and baseline characteristics

The demographics and baseline characteristics, medical history, prior and concomitant medications will be summarized by treatment group and overall for the FAS. Individual subject listings will be provided to support the summary tables.

8.4.1 Demographics

Age (years), height (cm), weight (kg), and other continuous demographic variables at Screening will be summarized descriptively. Gender, primary race, ethnicity, and other categorical variables will be summarized using FAS.

Year of birth, age, gender, race, ethnicity, height and weight will be listed as part of demographic listing.

8.4.2 Baseline characteristics

Tender joint counts [redacted] swollen joint counts [redacted] PGA of disease activity, PtGA of disease activity, total back pain, and nocturnal pain, MASES, ASQoL, SF-36, BASDAI, BASMI, BASFI, FACIT, SPARCC MRI Index of Disease Activity Score of the SI Joints and Spine, Modified Berlin ASspiMRI, ASDAS-CRP, ASDAS-ESR, hsCRP, ESR at baseline will be summarized. Rheumatoid factor and HLA B-27 at screening will be summarized as well.

8.4.3 Medical history

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using the most recently available version of the Medical Dictionary for Regulatory Affairs® (MedDRA). A listing of medical history will be provided as well.

Quantiferon testing and chest X-ray results at screening will be summarized using frequency counts for FAS.

8.4.4 Prior and concomitant medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary and categorized as the following:

Prior medications and concomitant medications will be summarized descriptively using frequency tables by ATC class and preferred name by treatment group on the Safety Analysis Set. Prior medications are those with a stop date before the first dose of study drug, and concomitant medications are those with a stop date on or after the first dose of study drug or ongoing.

Details for imputing missing or partial start and/or stop dates of medication are described in [redacted]

Prior biologic and prior anti-TNF medications will be summarized in a separate table.

8.5 Extent of exposure

8.5.1 Treatment Duration

Duration of study drug exposure (in days) will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Study drug exposure will be summarised by treatment group on the Safety Analysis Set using descriptive statistics.

Exposure to randomized study drug will also be categorised in intervals [redacted] and summarized by treatment group.

8.5.2 Treatment Compliance

Study drug compliance will be calculated as: [redacted] total number of doses administered /total

number of doses planned to be administered during the study drug exposure period. In case only one syringe among the two is administered at a visit, the number of doses will be counted as [redacted] If both syringes are administered at a visit, the number of doses will be counted as 1. The total number of doses planned will count Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 if a subject completes Part 1 and Part 2. If a subject discontinues treatment early, the total number of doses will be counted from Week 0 until the last dose before discontinuation.

Study drug compliance will be summarized by treatment group by the number of subjects (n), mean, SD, median, min, and max. They will also be summarized in categories [redacted]" and [redacted]" using frequency tables.

Study drug compliance summaries will be based on the Safety Analysis Set.

8.6 Efficacy analyses

8.6.1 Analysis methods

Analysis of proportions

The Cochran-Mantel-Haenszel (CMH) test, incorporating prior anti-TNF use as a stratification factor, will be used to compare response rates of response–type variables between the 200 mg tildrakizumab and placebo within AS and nr-axSpA separately. In addition, the Mantel-Haenszel common risk (the response rate) difference between 200 mg tildrakizumab and placebo and the 95% confidence interval (CI) will be estimated. Should assumptions per the Mantel-Fleiss criterion not be satisfied, the comparison will be based on a Fisher's exact test after collapsing across levels of the stratification factor. In this case, the response rate difference and CI will be based on a normal approximation without considering stratification.

Mixed model repeated measures analysis of continuous endpoints

A mixed model repeated measure (MMRM) analysis will be performed. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, visit, treatment-by-visit interaction, and prior TNF use (yes/no), as well as the continuous fixed covariate of baseline value. An unstructured matrix for the within-subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

In case of non-convergence with the unstructured matrix, other within-subject error variance-covariance matrices, such compound symmetry (CS), will be considered.

The model will provide least-squares mean estimates, standard errors, two-sided 95% confidence intervals and p-values (where applicable) for mean change at all time points between treatments (tildrakizumab vs. placebo).

8.6.1.1 Multiplicity

Not applicable.

8.6.2 Analysis of primary efficacy endpoint

The primary efficacy variable is ASAS20 at [redacted] ASAS20 will be analysed with CMH test as described in [redacted] for AS and nr-axSpA cohorts separately. Early withdrawals and any subjects with ASAS20 undeterminable at [redacted] will be classified as non-responders. Subjects who fail to show minimal response to treatment (defined as [redacted] improvement from Baseline in total back pain or inflammation) at [redacted] may have their background medications adjusted according to the maximum permitted daily dose described in the protocol and continue in the study. Any subject requiring these adjustments will be counted as a non-responder for the primary analysis.

The sample SAS codes are:

[redacted]

To assess the robustness of the primary efficacy analysis, sensitivity analysis will be repeated with the PPAS.

Subgroup analysis will be performed for each of the following subgroup variables:

- Prior anti-TNF use (Yes/No)
- Baseline weight (≤ 90 kg, > 90 kg)
- Age (< 65, ≥ 65)
- Gender
- Methotrexate use (Yes/No)

The sample SAS codes for anti_TNF subgroup analysis are:

[redacted]

Estimates of the difference between the treatment groups, along with the [redacted] (but no p-value needed), will be presented for each defined category of each subgroup variable.

If sample size for a category of a subgroup factor is too small, the analysis for that subgroup may not be performed.

The primary purpose of the subgroup analyses is to check for consistency of results across factors of interest.

8.6.3 Analysis of secondary endpoints

All secondary analyses will be performed using the FAS, unless otherwise stated. Proportions in ASAS40 at Weeks 24 will be analyzed based on the CMH method described for ASAS20 in primary analysis. Due to the placebo group switching to 200 mg tildrakizumab at [redacted], the comparison between active drug and placebo will not be performed for the secondary endpoints collected after [redacted]. ASAS20 and ASAS40 up to [redacted] will be summarized with descriptive statistics.

Analysis on ASAS40 at [redacted] will also be performed for the PPAS.

8.6.4 Analysis of exploratory endpoints

The response-type endpoints (ASAS20/40 at other measurement time points, ASAS70, ASAS5/6 up to [redacted] and proportion of subjects who require adjustment of background therapy at Week 16 will besummarized with descriptive statistics. Continuous endpoints (change from baseline in PtGA of disease activity, Total Back Pain, Nocturnal Pain, Inflammation, BASFI, BASMI, BASDAI, ASQoL, ASDAS-CRP, ASDAS-ESR, MASES, SF-36, FACIT-fatigue, TJC46, SJC44, hsCRP, SPARCC MRI Index of Disease Activity Score of the SI Joints, SPARCC MRI Index of Disease Activity Score of the Spine, and Modified Berlin ASspiMRI) up to [redacted] will be analyzed based on a MMRM analysis that includes the fixed effects of treatment, visit, treatment by visit interaction, prior anti-TNF use (yes/no), and Baseline value. Due to placebo group switching to 200 mg Tildrakizumab at [redacted], the comparison between active drug and placebo will not be performed for the exploratory endpoints collected after [redacted]. Continuous endpoints after [redacted] be summarized descriptively.

Below is an example of the SAS code for the MMRM

[redacted]

For [redacted], the proportions of subjects who achieve ASAS20, ASAS40, ASAS70, and ASAS5/6, at each measured time point during [redacted] will be summarized by treatment

group; change from Baseline in PtGA of disease activity, Total Back Pain, Nocturnal Pain, Inflammation, BASFI, BASMI, BASDAI, MASES, SF-36, FACIT-fatigue, TJC46, and SJC44 during Weeks 53 to 72 will be summarized descriptively by treatment group. In addition, there will be sub-groups of patients in Part 3 who either did or did not receive any new therapy for AS and these will be analyzed separately for ASAS20, ASAS40, and ASAS70.

All the exploratory analyses will be based on the FAS.

8.7 Safety analyses

Safety analyses will be conducted on the Safety Analyses Set (treated subjects) and will be performed for all safety variables specified below.

All safety data will be summarized by treatment group.

The safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters, vital signs, and ECG) will only include subjects from the Safety Analysis Set who have data available for both the baseline and the time point under consideration unless otherwise specified.

No statistical test will be performed.

8.7.1 Adverse events

All AEs will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the most recently available version of the MedDRA dictionary.

In summaries by SOC and PT, adverse events will be sorted within each SOC and PT in alphabetical order. In summaries by PT, AEs will be sorted within each PT in alphabetical order.

Details for imputing missing or partial start dates of adverse events are described in [redacted]

TEAEs are defined as any AE occurring or worsening on or after the first dose of IMP. AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- Related TEAEs (AE will be defined as related if causality is possibly, probably, or certain)
- TEAEs by maximum severity
- TEAEs leading to discontinuation
- Serious TEAEs
- TEAEs leading to death.

An overall summary for the categories above will be prepared by study part, treatment group and overall. A TEAE in Part 1 is defined with the event start date on/after the first dose but before [redacted] dosing date of IMP or on/before the last dose date of IMP if the subject discontinues before [redacted] A TEAE in Part 2 is defined with the event start date on/after [redacted] dosing

date but on/before the last dose date of IMP. A TEAE in Part 3 is defined with the event start date after the last dose date of IMP.

In addition, all TEAEs will be summarized by study part (Parts 1, 2, 3), SOC, PT and treatment group using frequency counts and percentages (i.e., number and percentage of subjects with an event).

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in a specific study part, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in a specific study part, the subject will only be counted once at the system organ class level in adverse event frequency tables.

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary table will also be provided based on the most intense event - independent of relationship to study treatment.

Adverse Events of Special Interest (AESIs)

The events of severe infections, malignancies (including non-melanoma and melanoma skin cancer, excluding carcinoma in situ of the cervix), confirmed Major Adverse Cardiac Events (MACE), and drug-related hypersensitivity reactions will be identified a priori as AESIs for summarizing in this study. Severe infections are defined as any infection meeting the regulatory definition of a SAE, or any infection requiring IV antibiotics whether or not reported as a serious event, as per the regulatory definition. Major Adverse Cardiac Events include non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death. All MACE events will be evaluated and adjudicated by a Clinical Adjudication Committee. The AESIs will be summarized by study part, SOC, PT and treatment group.

Events of Clinical Interest (ECIs)

An ECI is a non-serious AE or occurrence that is designated to be of special interest and must be reported to the Sponsor as though it were an SAE. The ECIs will be summarized by study part, SOC, PT and treatment group.

The following events are considered ECIs for this study:

1. An overdose of the Sponsor's product, as defined as any dose greater than the intended protocol dose. An overdose that is not associated with clinical symptoms or abnormal laboratory results is to be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

2. An elevated AST or ALT laboratory value that is [redacted] the ULN and an elevated total bilirubin laboratory value that is [redacted] ULN and, at the same time, an alkaline phosphatase laboratory value that is [redacted] ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing, is to be reported as a non-serious ECI.
3. Infections that require IV antibiotics but do not meet the definition of an SAE will be designated a closely monitored AE for this study.
4. Depression and suicidal ideation and behavior events.

In addition, a listing containing individual subject adverse event data for TEAEs leading to discontinuation from study, Serious TEAEs, TEAEs leading to death, AESIs, and ECIs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in an individual subject data listing.

8.7.2 Clinical laboratory evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units. If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

Clinical laboratory parameters observed values and changes from Baseline will be summarized at each scheduled visit. Shift table from baseline to post-baseline in lab parameters for each treatment group during Part 1 will be displayed by visit.

Values outside the normal range will be categorized as H (above the normal range) or L (below the normal range) based on the laboratory's reference range and these will be flagged in the listings of individual subject data.

8.7.3 Vital signs

Vital sign observed values and changes from Baseline will be summarized at each scheduled visit.

A listing of vital signs by subject will be produced.

8.7.4 Physical examinations

Physical examination results will be summarized with incidence of "Normal" and "Abnormal" by body system at each scheduled visit. All physical examination data and abnormalities will be listed.

8.7.5 Electrocardiograms

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with "Normal", "Abnormal, not clinically significant", and "Abnormal, clinically significant". In addition, shift table from baseline to post-baseline in overall ECG interpretation during Part 1 will be displayed by visit and treatment group.

ECG parameter (e.g., QTcF) observed values and changes from Baseline will be summarized at each scheduled visit.

An accompanying listing of subjects will be produced and it will display all ECG findings during the study in subjects with abnormal ECGs, as determined by the investigator.

8.7.6 Assessment of Suicidal Ideation and Behavior

Subjects will be assessed for suicidal ideation and behavior at the Screening Visit using the Baseline (Lifetime) C-SSRS, and each subsequent visit using the C-SSRS Since Last Visit version.

The C-SSRS consists of 2 major aspects: Suicidal Ideation and Suicidal Behavior. Based on outcomes and data analyses suggested by the C-SSRS website, the following endpoints will be used to analyze C-SSRS data:

- Presence of Suicidal Ideation: Set to 1 if any ideation is present and 0 otherwise.
- Presence of Suicidal Behavior: Set to 1 if any type of suicidal behavior is present and 0 otherwise.
- Suicidal ideation score: Defined as the maximum suicidal ideation category (1-5) on the C-SSRS present at the assessment. A score of 0 is assigned if no ideation is present.

The number (%) of subjects with presence of suicidal ideation/behavior will be summarized at each assessment time. The C-SSRS data will be summarized using worst-case shift tables. Worst-case shift tables will be the cross tabulation of the Baseline result score with the worst-case result score during the treatment period.

8.8 Other analysis

8.8.1 Analysis of Pharmacokinetic Endpoints

Plasma tildrakizumab concentration data will be listed by individual subject and summarized by time.

PK parameters of AUC, C_{max}, C_{min}, T_{max}, and $T_{1/2}$ will be summarized with descriptive statistics (n, mean, SD, geometric mean, coefficient of variation [%CV], minimum, first, second (i.e., median) and third quartiles, and maximum).

The PK Analysis Set will be used for the analysis.

Exploratory PK analyses will be performed by another vendor and described in a separate SAP.

8.8.2 ADA to Tildrakizumab

For each subject, tildrakizumab serum concentrations and ADA sample results are matched to actual sampling times and treatment. Subjects are grouped based on the actual treatment received, rather than the treatment group at randomization. Subjects have baseline samples taken prior to

dosing to assess for any preexisting immune response that may be detected by the ADA assays. Subjects are considered positive if at least one pre-treatment or post-dose sample is positive at any time. Positive subjects are subsequently categorized into treatment-emergent positive if the positive sample occurs following treatment with tildrakizumab or non-treatment emergent positive if the subject has an immune response present at baseline and the response is not boosted following treatment.

The presence of tildrakizumab can interfere with the ADA assay at concentrations above the drug tolerance level (DTL) of [redacted]. Therefore, samples with a negative test result in the ADA assay can only be described as negative in the case of a tildrakizumab concentration below 6 µg/mL. The immunogenicity status of a subject is considered to be negative if all pre-treatment and post-dose samples tested negative in the ADA assay and if the concentration of tildrakizumab in the last post-dose sample is below the DTL. Therefore, an integrated evaluation of ADA results and drug serum concentrations is required for interpretation of immunogenicity results.

To summarize, subjects are categorized in one of four immunogenicity categories as described in Table 3. The overall immunogenicity incidence is defined as the proportion of treatment-emergent positive subjects to the number of evaluable subjects. The proportion of non-treatment emergent positive subjects is similarly reported. For ADA positive subjects (based on the confirmatory assay), the immune response is further characterized for antibody titer and neutralizing capacity. When titer is measured to be [redacted] for the purposes of deriving ADA subject status.

Table 3 Immunogenicity Subject Status Definitions

Subject Status	Definition
Negative	All pre-treatment and post-dose samples were negative in the ADA assay and the drug concentration in the last post-dose sample was below the respective DTL [redacted] for the ADA assay.
Inconclusive	All pre-treatment and post-dose samples were negative in the ADA assay AND the drug concentration in the last post-dose sample was equal or above the respective DTL for the ADA assay.
Treatment-emergent Positive	Pre-treatment sample was negative and at least 1 post-dose sample was positive in the ADA assay (treatment-induced positive).
	Pre-treatment and post-dose samples were both positive in the ADA assay and the titer increased post-dose by ≥2-fold (treatment boosted positive).
Non-treatment-emergent Positive	Pre-treatment sample was positive and post-dose samples were negative in the ADA assay.
	Pre-treatment and post-dose samples were positive in the ADA assay with a < 2-fold increase in titer post-dose
ADA = anti-drug antibodies; DTL = drug tolerance level.	

The anti-tildrakizumab immunogenicity status of evaluable subjects, along with titer and neutralizing antibody, will be summarized by dose level in Part 1. Only data from Part 1 is used and placebo samples in Part 1 are excluded. The anti-tildrakizumab immunogenicity status of

evaluable subjects will be further summarized by treatment group and by dose level for Parts 1 and 2 combined. ADA data will be presented in a listing.

8.8.3 Correlation of ADA with Pharmacokinetics

Mean plots of tildrakizumab concentration (µg/mL) versus time for ADA positive and ADA negative or inconclusive during Part 1 and Part 2 will be displayed for subjects in groups of tildrakizumab 200 mg and placebo → 200 mg Tildrakizumab, respectively.

8.8.4 ADA to Efficacy Endpoints

The impact of ADA on the responder type of efficacy endpoints (ASAS20 and ASAS40) will be summarized by dose level for Part 1. Only data from Part 1 is used and placebo samples in Part 1 are excluded.

8.9 Interim analysis

An interim analysis (IA) will be performed for futility assessment after data at Week 16 from 30 randomized subjects become available. Futility assessment will be based on a futility threshold of 12% (difference between response rates on active arm and placebo) at Week 16. The purpose of the analysis is potentially to stop for futility. If the difference between response rates of ASAS20 for tildrakizumab 200mg and placebo is less than the threshold of 12%, the study may be stopped for futility. The conditional power of rejecting the null ASAS20 hypothesis will be calculated with ADDPLAN software.

Following the last subject's Week 24 visit, an IA will be conducted on all available data up to Week 24 to evaluate the primary efficacy outcome. The primary endpoint ASAS20 and selected other endpoints will be included in the IA.

Details of the IA methodology and operational processes will be described in a separate document.

9 REPORTING CONVENTION

This section details the format and layout of all TFLs and statistical output that will be produced in conjunction with the Clinical Study Report. The table of contents and templates for the TFLs will be produced in a separate document.

All data analyses and generation of TLFs will be performed using SAS 9.4® or higher.

The following reporting conventions will be adopted for the presentation of study data:

- The tables and listings will be provided in a Word document in landscape format, [redacted] The output alignment will be centered on the page and the titles and footnotes will be center aligned.
- The ICH[1,2] numbering convention will be used for all TLFs.
- The analysis population represented on the tables will be clearly identified in the title of the table.
- Dates will appear as DDMMMYY format; times as HH:MM format (24 hour clock).
- For the presentation of summary data, results will be aligned on the decimal point and be centered within the column. Unless otherwise stated, tables will summarize the results per treatment group (Active treatment, Placebo) and overall.
- All TLFs will have the SAS program path and name, output filename and date/time of production in the footnote, and will include the following hierarchy of titles and footnotes (as an example):

[redacted]

10 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

The sponsor decided not to do PK and ADA analysis due to the study termination.

11 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
3. Ware JE. User's Manual for the SF-36v2 Health Survey; 2007.

12 APPENDICES

12.1 Endpoint definition and Derivation Details

12.1.1 [redacted]

The [redacted] is a multi-purpose, 36-item survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these 8 domains and 2 summary measures of physical and mental health. All domains and summary components are scored such that a higher score indicates a higher functioning or health level.

These 8 domains are as follows:

a. Physical Functioning (PF). This score is based on the responses to the 10 items that compose Question 3 and reflects the degree to which various physical activities have been limited in the previous week by the subject's health.

b. Role-Physical (RP). This score is based on the responses to the four items that compose Question 4 and reflects the relative amount of time that the subject has had problems with work or other regular daily activities as a result of their physical health during the previous week.

c. Bodily Pain (BP). This score is based on the responses to Questions 7 and 8 and reflects bodily pain and its effects on normal work during the previous week.

d. General Health (GH). This score is based on responses to Question 1 and the four items in Question 11 and reflects the subject's perception of their general health during the previous week.

e. Vitality (VT). This score is based on responses to Question 9 items a, e and g, and reflects the subject's physical energy level relative to time during the previous week.

f. Social Functioning (SF). This score is based on responses to Questions 6 and reflects how physical health or emotional problems have interfered with social activities during the previous week.

g. Role-Emotional (RE). This score is based on responses to the three items in Question 5 and reflects the amount of time during the previous week that emotional problems have interfered with work or regular daily activities.

h. Mental Health (MH). This score is based on responses to Question 9 items b, c, d, f, and h and reflects various mental/emotional states relative to time during the previous week.

The summary component scores are:

a. Physical Component Summary (PCS).

b. Mental Component Summary (MCS).

Data Derivation Details to Obtain Scale Scores for SF-36

VARIABLE	DERIVATION
SF-36 PF scale score	[redacted] When calculating the raw score, if [redacted] or more of the items are non-missing then replace any missing values as follows: Calculate the mean of the answered questions, using the number of answered questions as the denominator. Substitute the mean for any missing scores. Otherwise, if [redacted] of the items are non-missing then PF scale score is missing. The response scale for each activity ranges from [redacted] A higher PF scale score indicates better physical functioning.
SF-36 RP scale score	[redacted] When calculating the raw score, if [redacted] or more of the items are non-missing then replace any missing values as follows: Calculate the mean of the answered questions, using the number of answered questions as the denominator. Substitute the mean for any missing scores. Otherwise, if less than [redacted] the items are non-missing then RP scale score is missing. The response scale for each item ranges from [redacted] A higher RP scale score indicates better role-physical functioning.

VARIABLE	DERIVATION
SF-36 BP scale score	[redacted] If 1 or more questions were answered, calculate BP scale score as defined above. If neither question was answered then BP scale score is missing. The scale for [redacted]. The scale for [redacted] A higher BP scale score indicates lack of bodily pain.

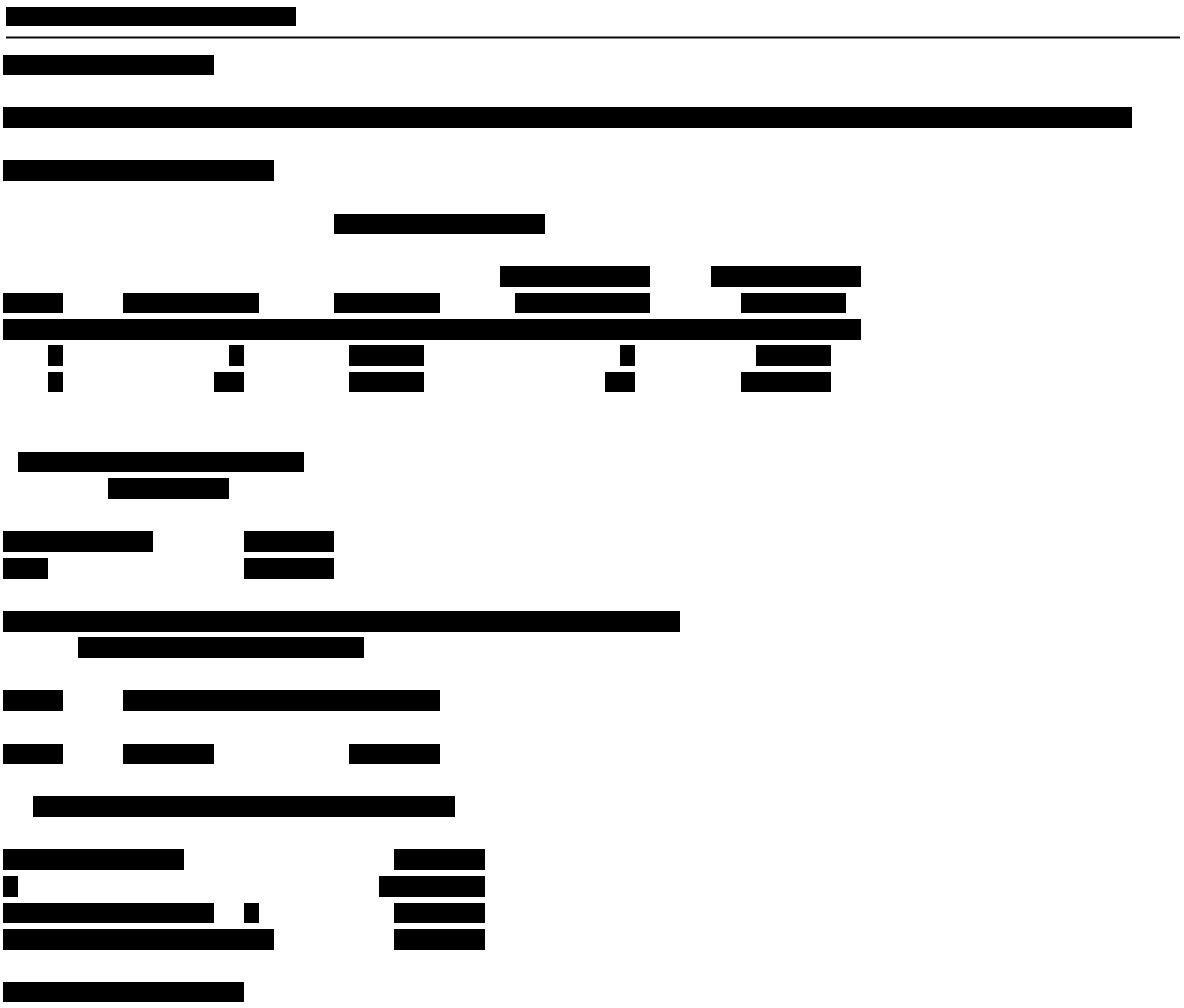
VARIABLE	DERIVATION
SF-36 GH scale score	[redacted] Reverse direction of Item 1 as follows: [redacted] Reverse direction of item [redacted] by subtracting score from 6. When calculating the raw score, if [redacted] or more of the items are non-missing then replace any missing values as follows: Calculate the mean of the answered questions, using the number of answered questions as the denominator. Substitute the mean for any missing scores. Otherwise, if [redacted] of the items are non-missing then GH scale score is missing. Responses for [redacted] Responses for the items in [redacted] and reflect the subject's perception of their relative health and expectations of their future health status. A higher GH scale score indicates better general health perceptions.

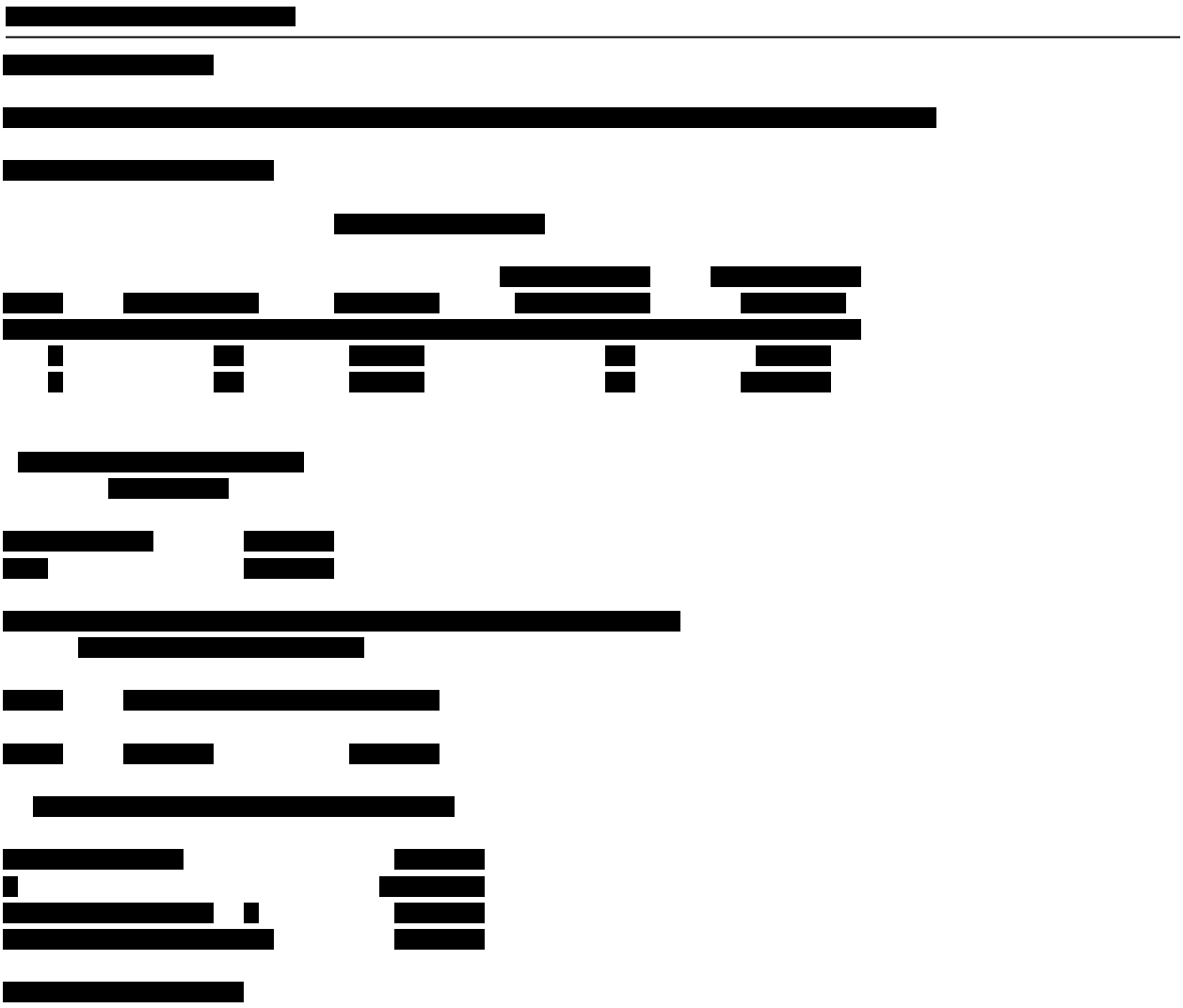
VARIABLE	DERIVATION
SF-36 VT scale score	[redacted] Reverse direction of Items [redacted] by subtracting score from [redacted]. When calculating the raw score, if [redacted] or more of the items are non-missing then replace any missing values as follows: Calculate the mean of the answered questions, using the number of answered questions as the denominator. Substitute the mean for any missing scores. Otherwise, if [redacted] of the items are non-missing then VT scale score is missing. The scale for these items ranges from [redacted]
SF-36 SF scale score	[redacted] Reverse direction of [redacted] When calculating the raw score, if [redacted] of the items is missing then substitute the missing score with the score on the non- missing item. If both items are missing then SF scale score is missing. Responses to [redacted] an assessment of the extent to which health/emotional problems interfered with social activities. [redacted] A higher SF scale score indicates better social functioning.

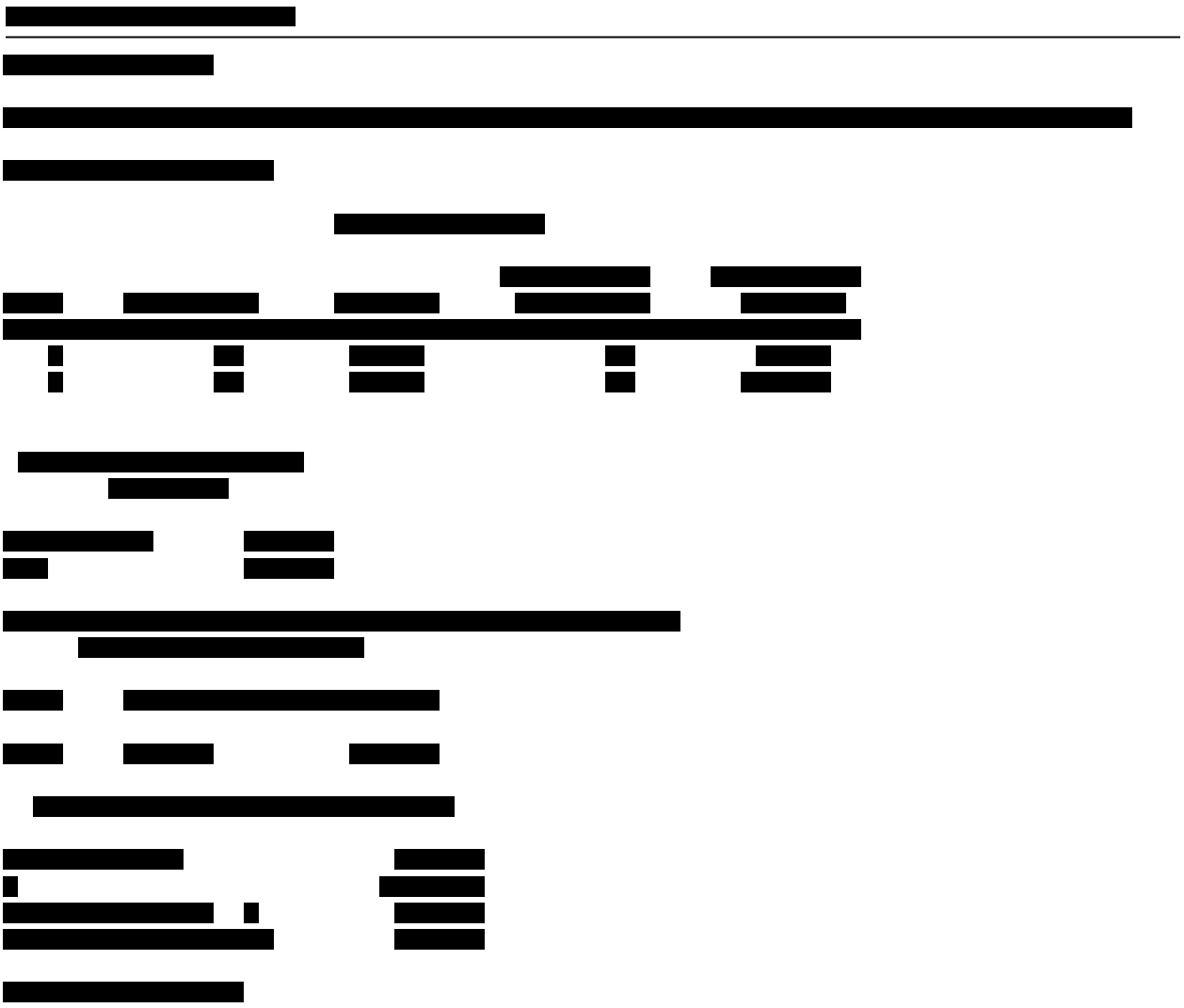
VARIABLE	DERIVATION
SF-36 RE scale score	[redacted] When calculating the raw score, if [redacted] or more of the items are non-missing then replace any missing values as follows: Calculate the mean of the answered questions, using the number of answered questions as the denominator. Substitute the mean for any missing scores. Otherwise, if [redacted] 2 of the items are non-missing then RE scale score is missing. Responses to the items in [redacted]
SF-36 MH scale score	[redacted] Reverse direction of scores for 9D and 9H, by subtracting score from 6. If 3 or more of the items are non-missing then replace any missing values as follows: Calculate the mean of the answered questions, using the number of answered questions as the denominator. Substitute the mean for any missing scores. Otherwise, if [redacted] of the items are non-missing then MH scale score is missing. The scale for these items ranges from [redacted]

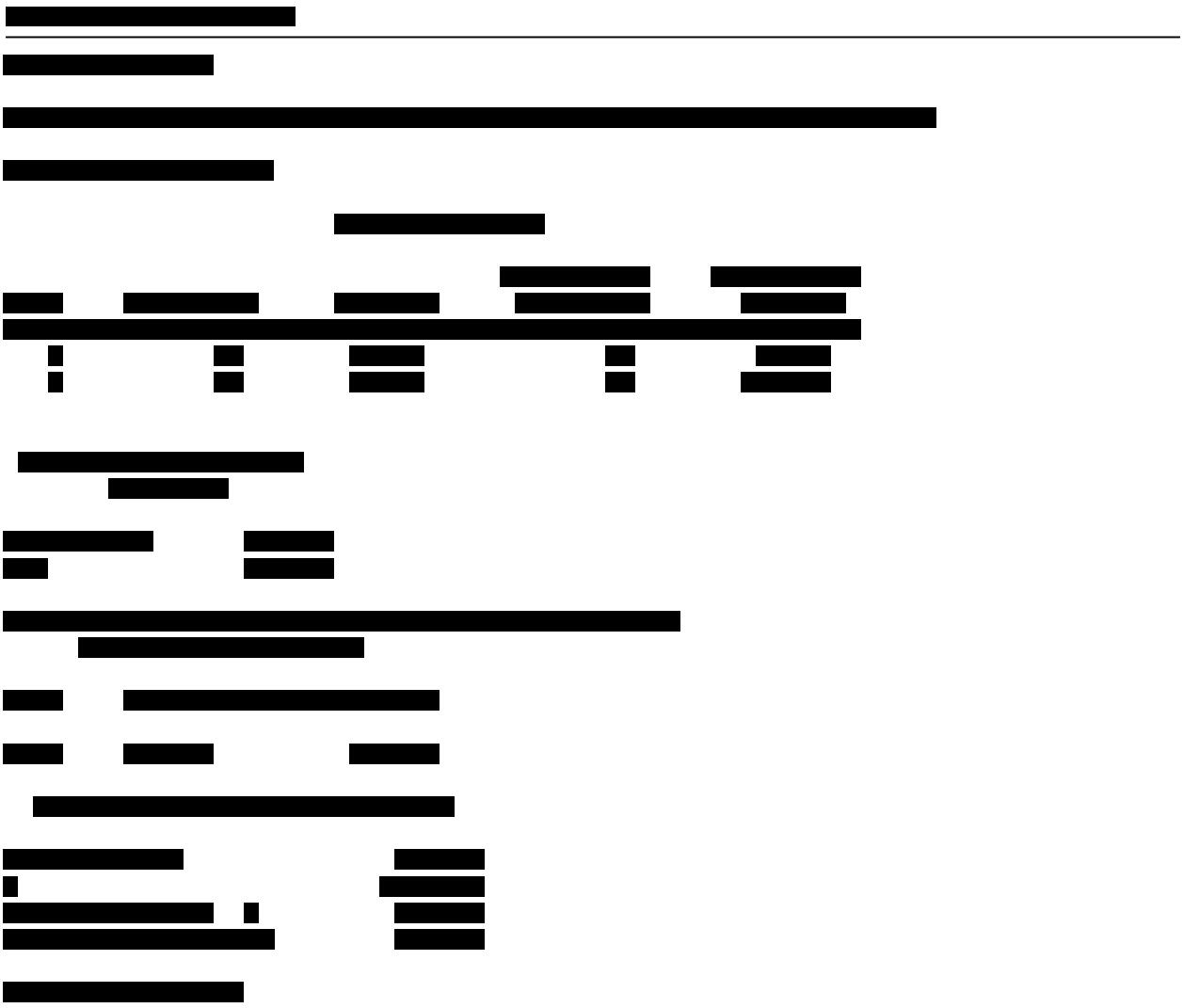
VARIABLE	DERIVATION
[redacted]	[redacted]
[redacted]	[redacted]

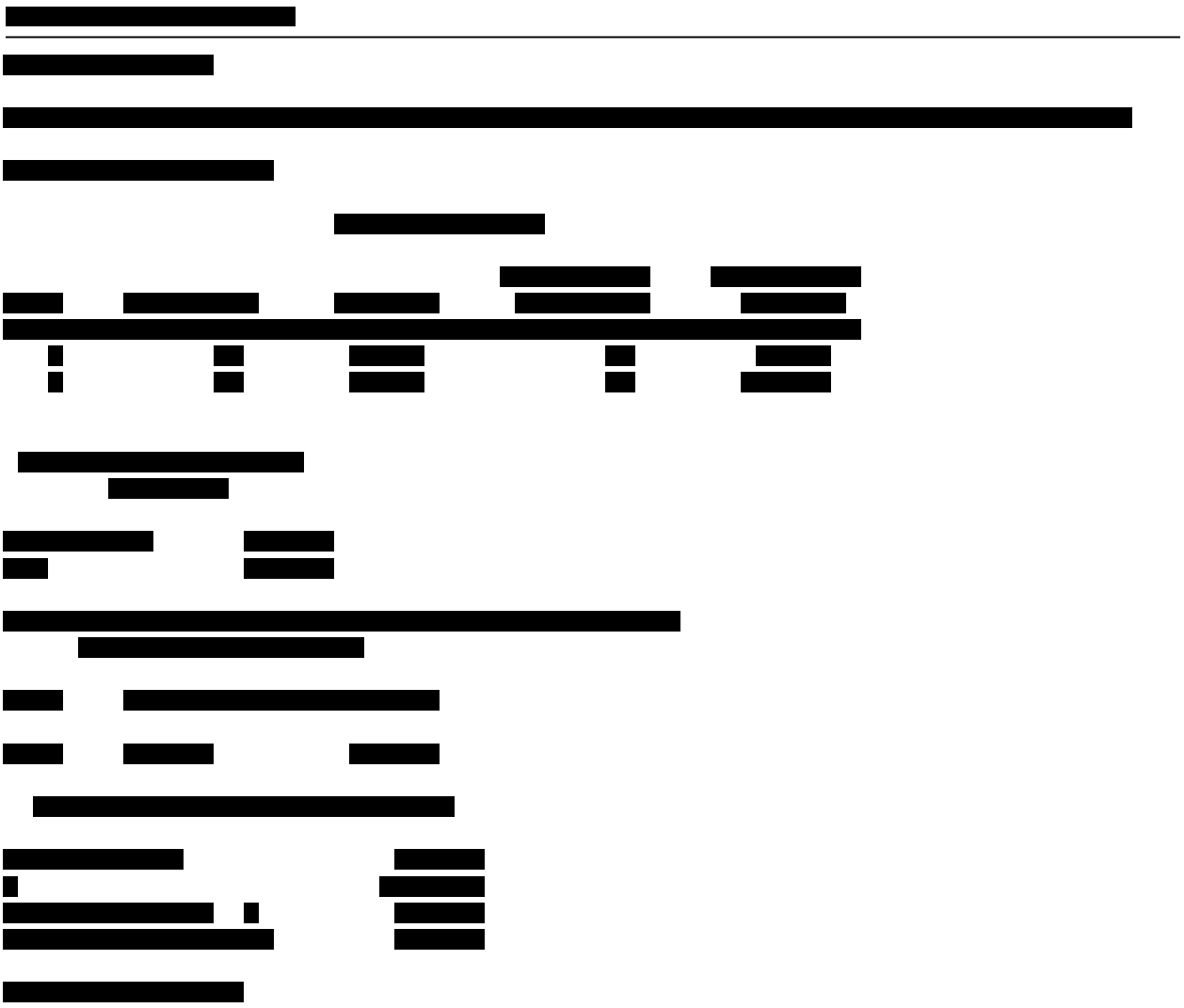
VARIABLE	DERIVATION
SF-[redacted] MCS score	[redacted]

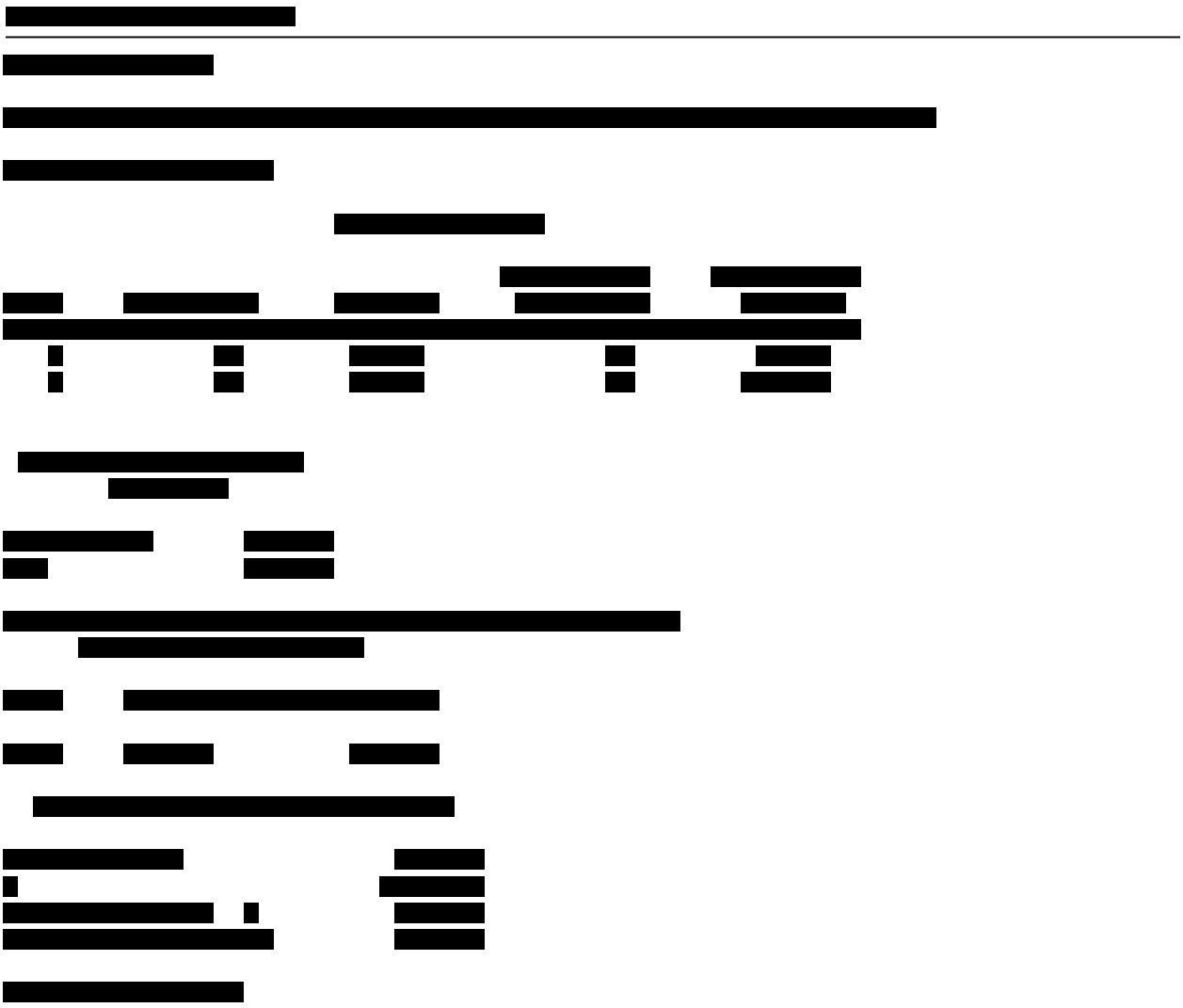


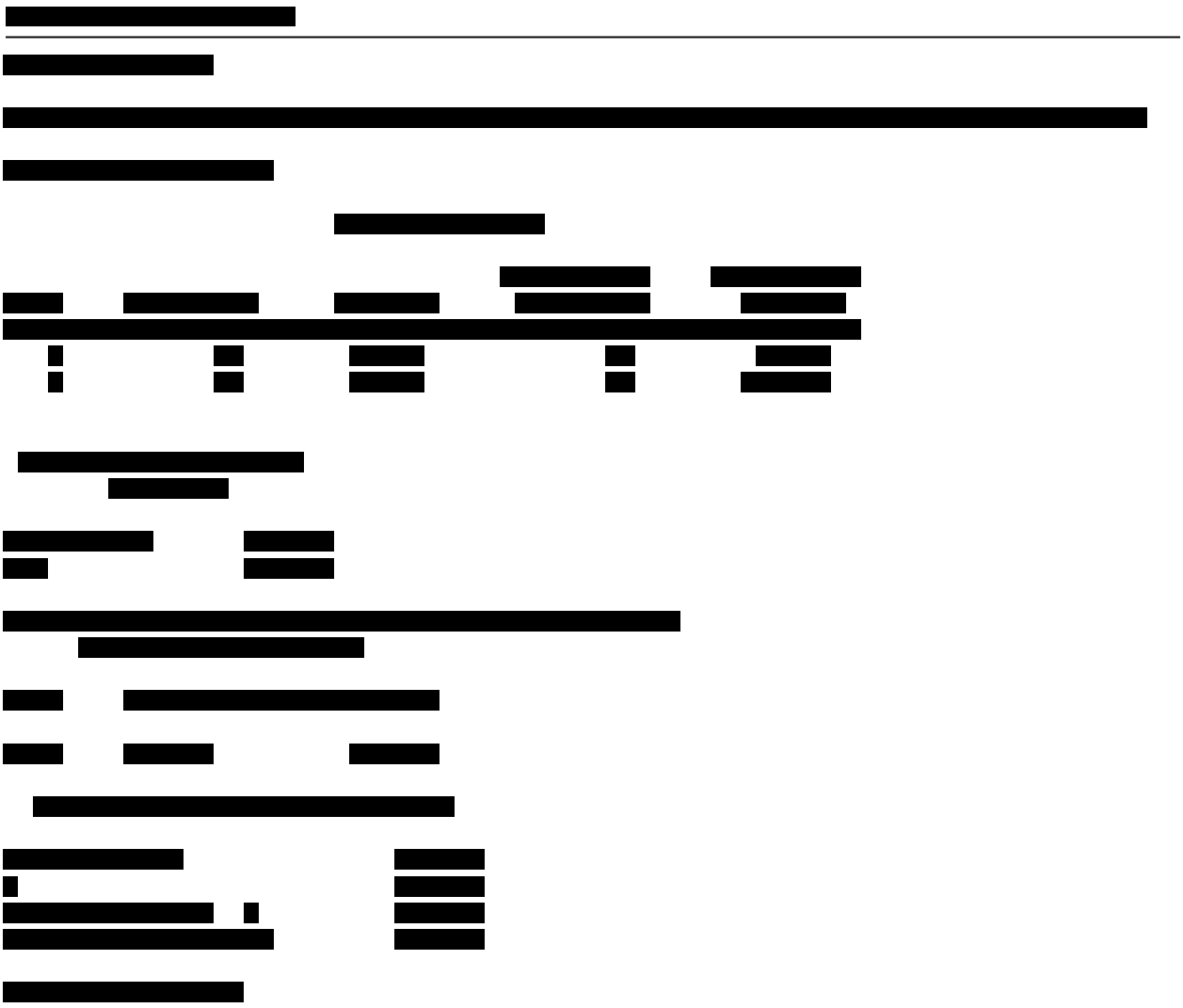


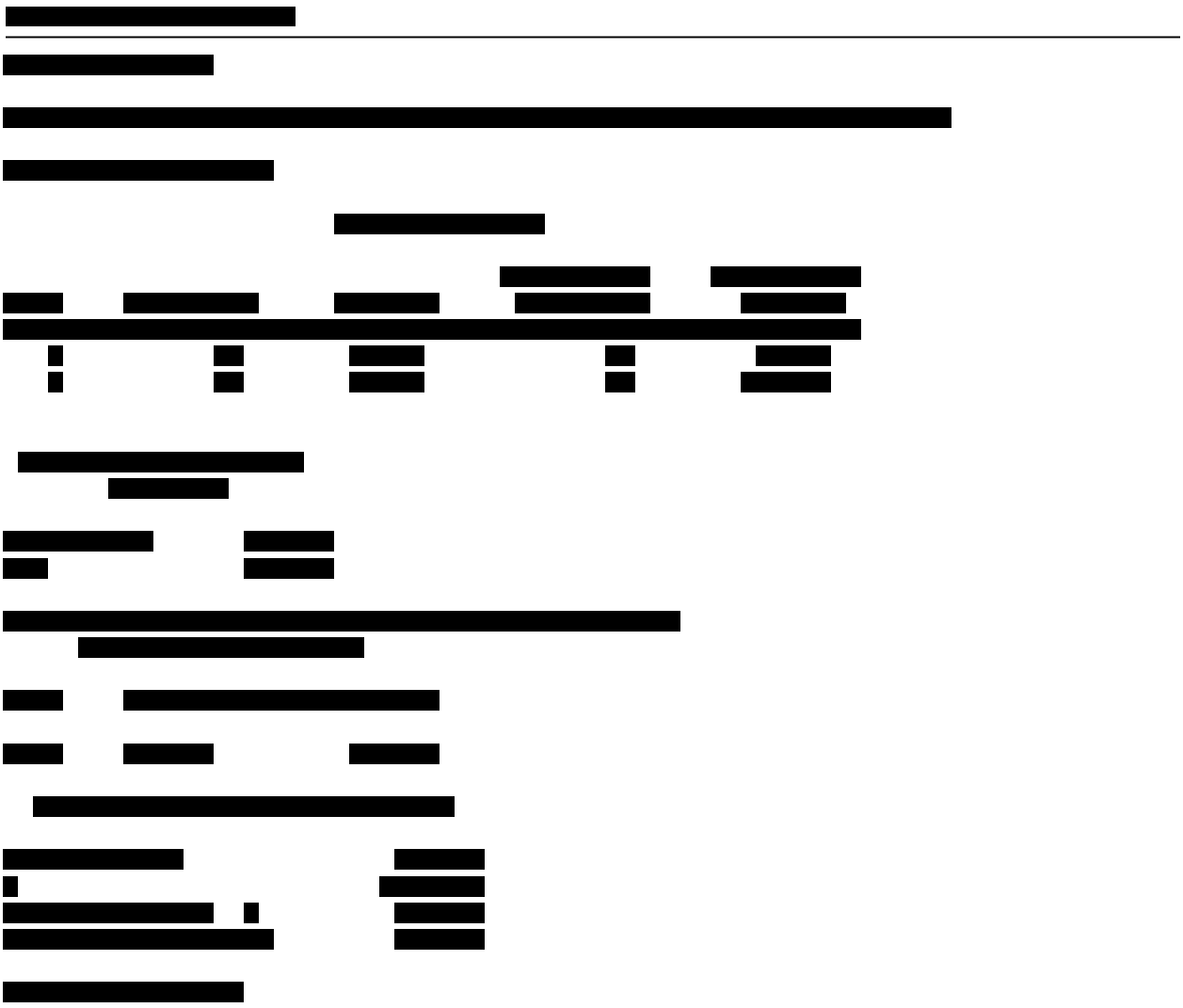


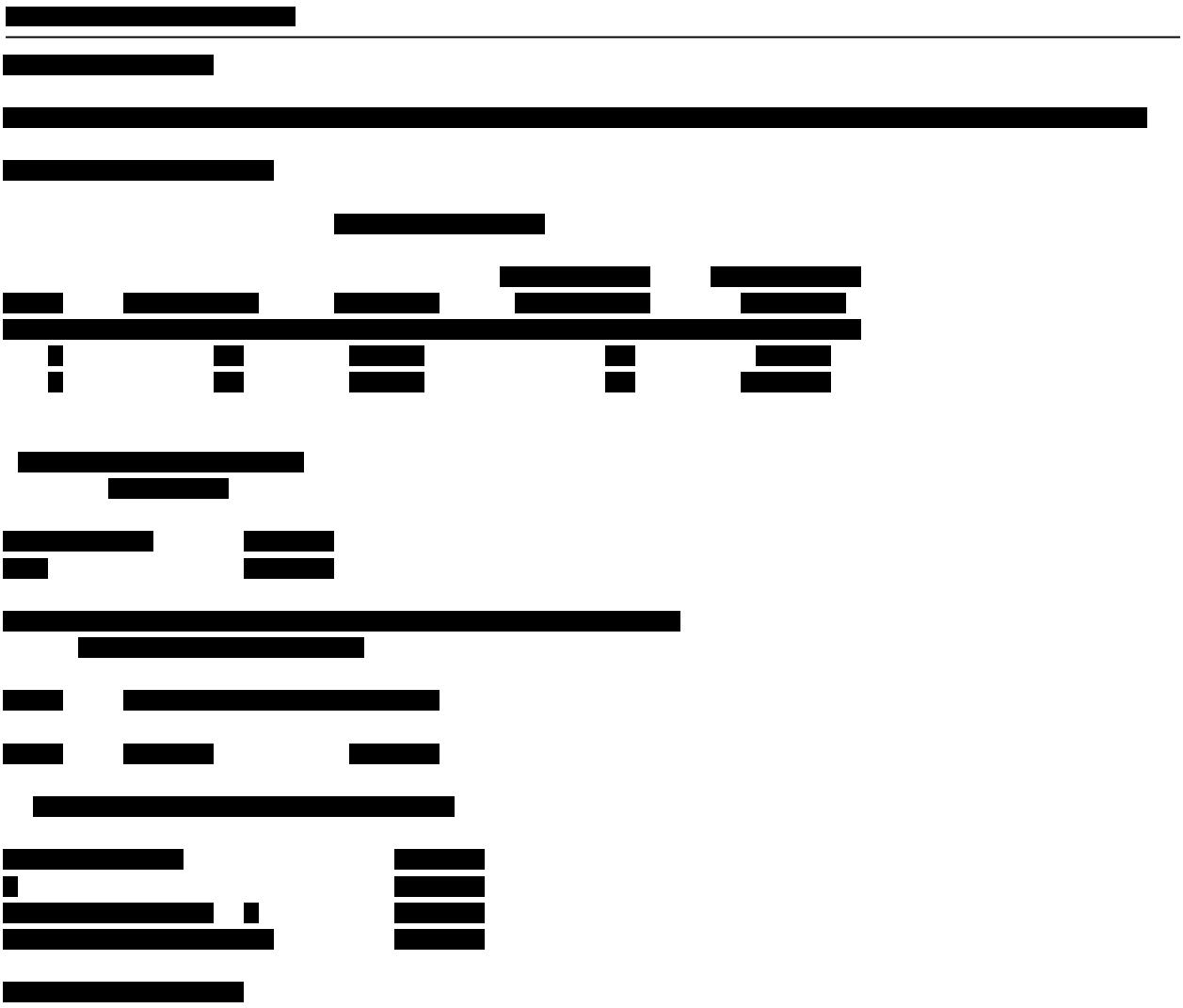


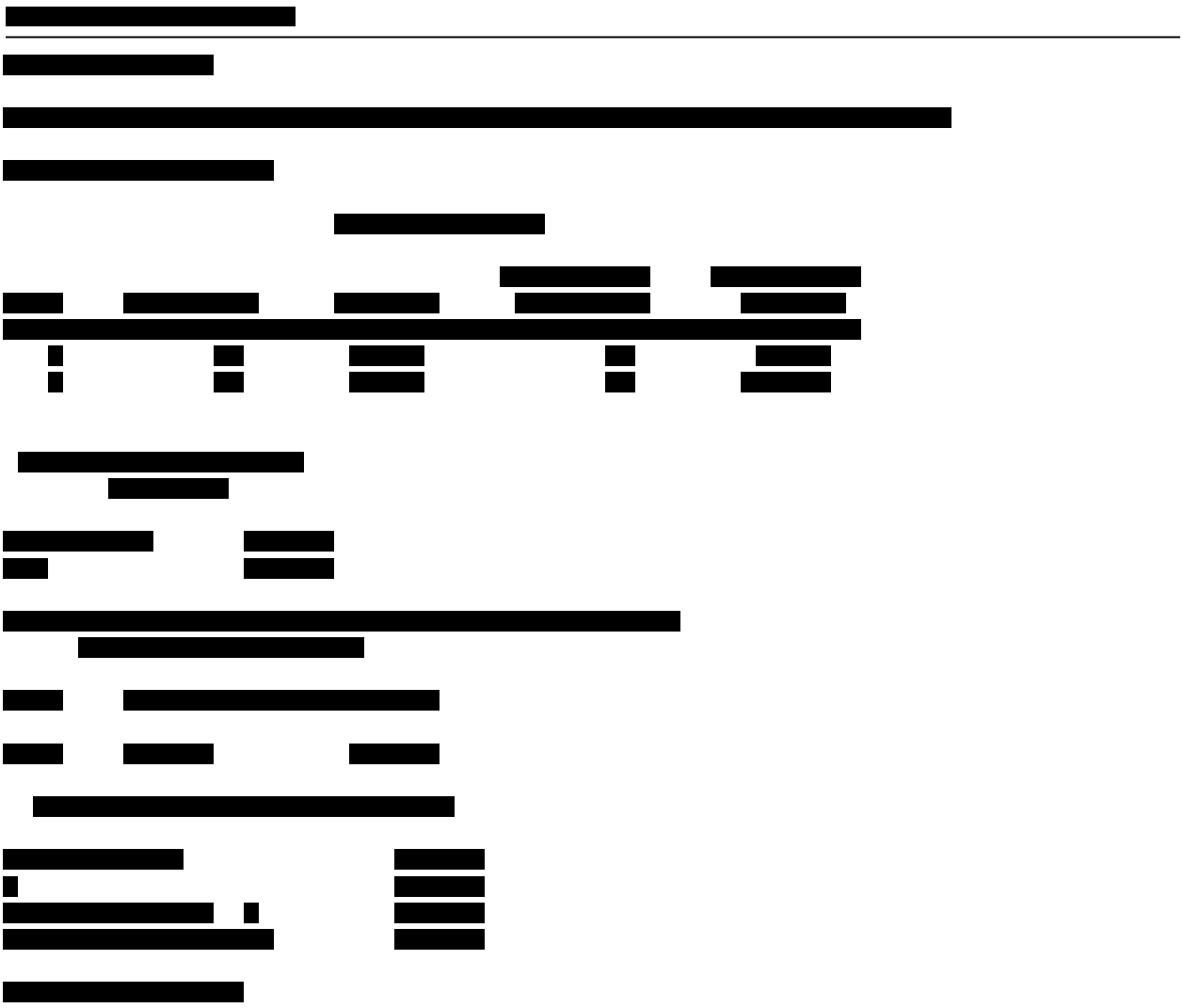


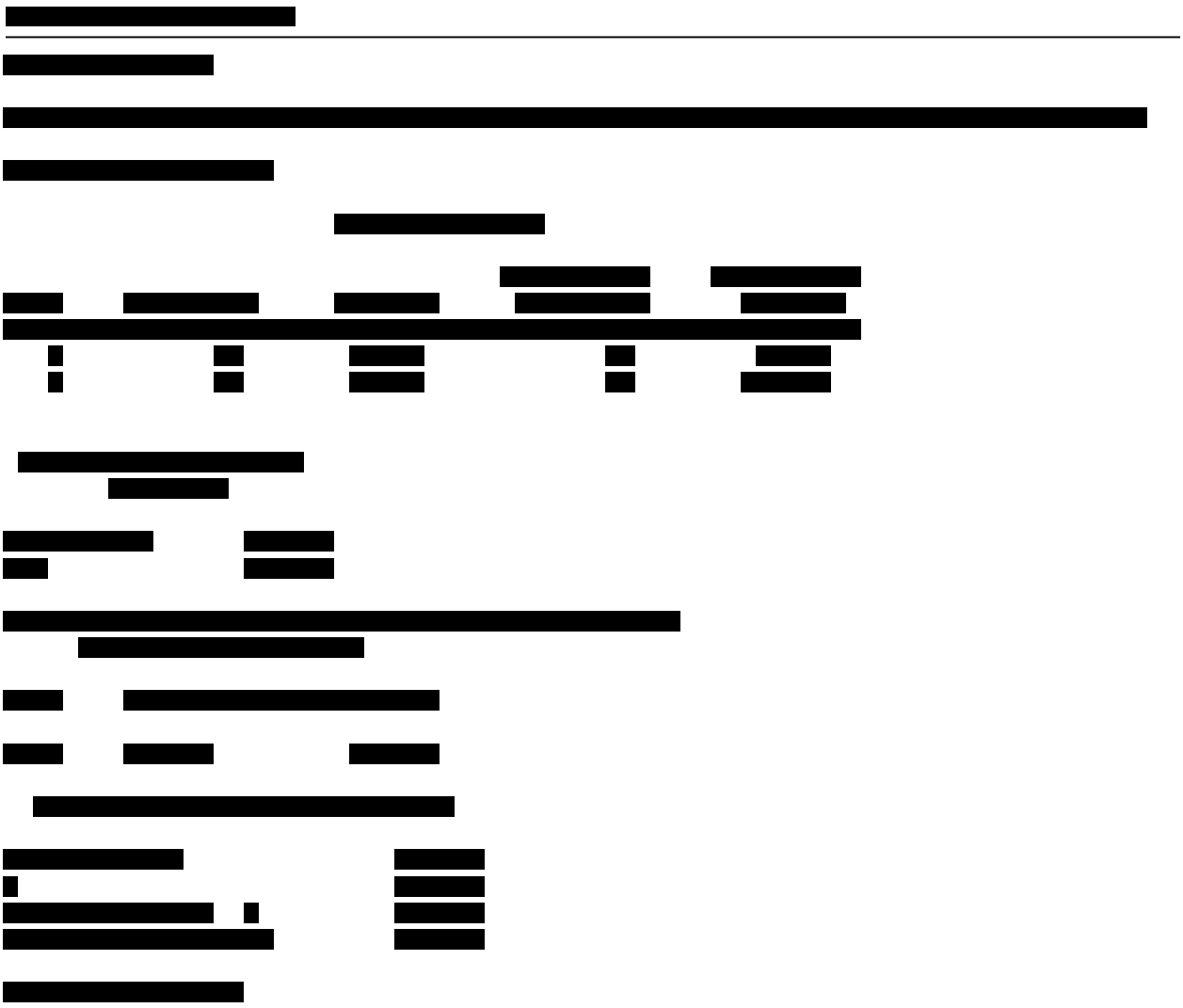


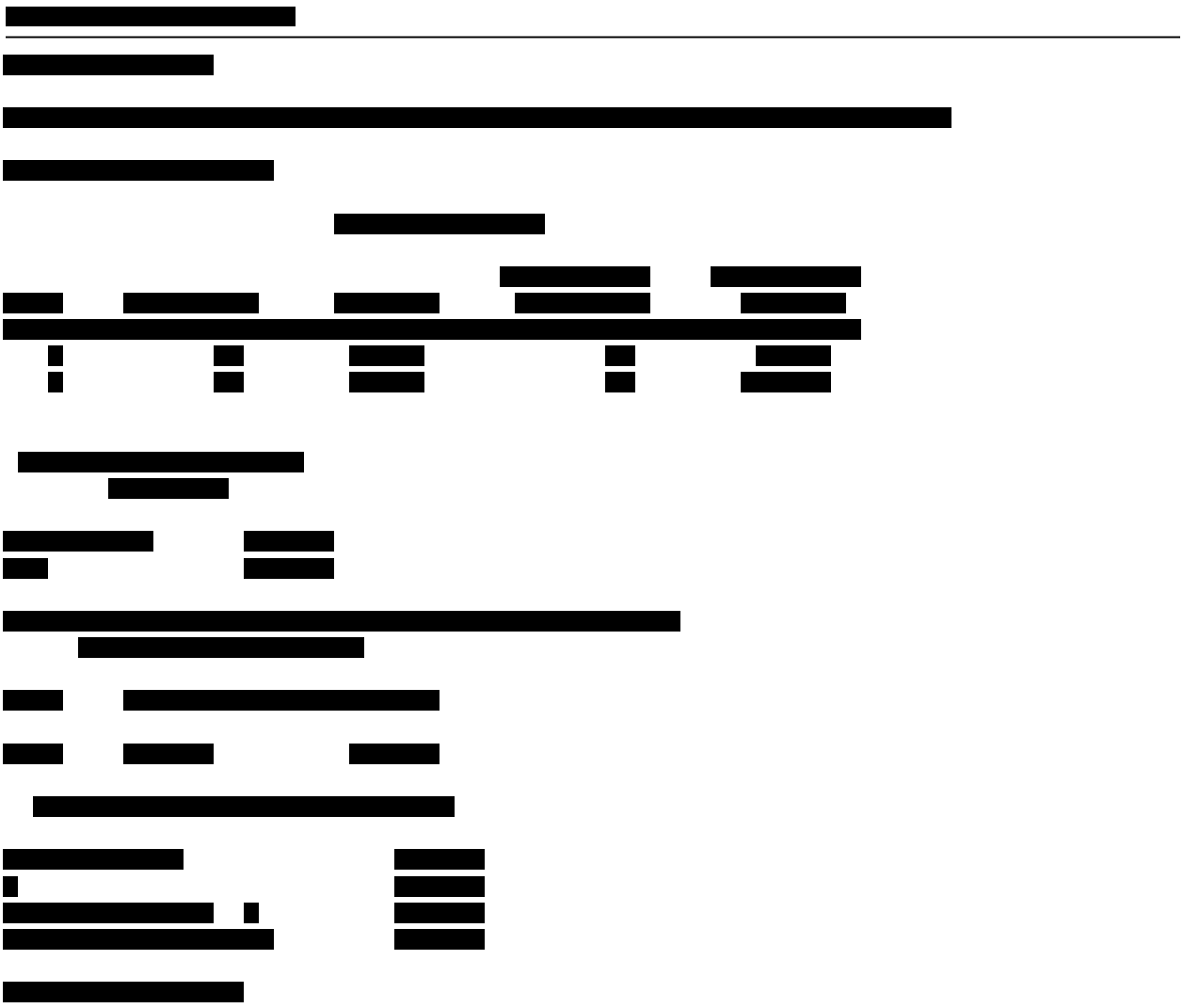


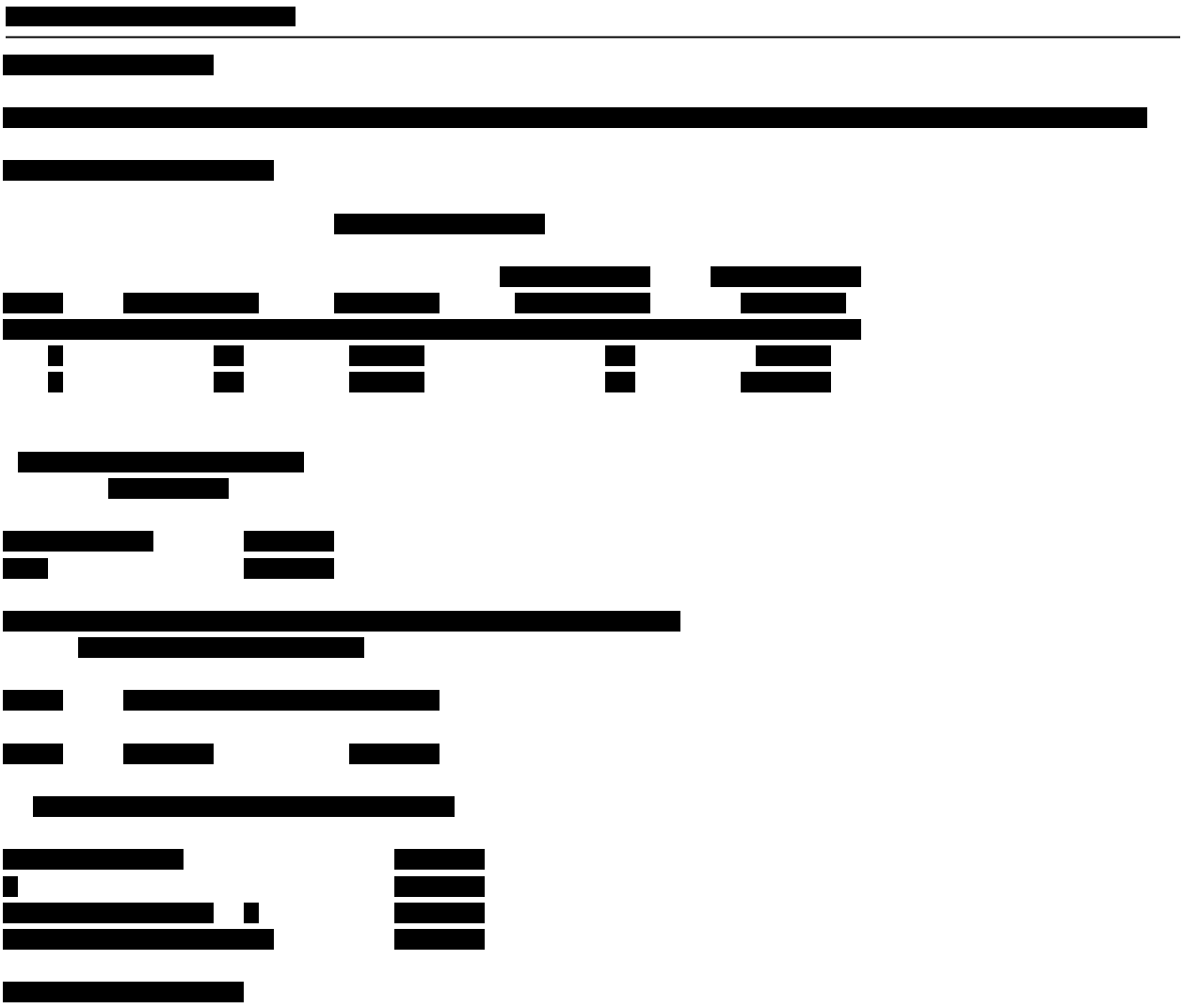


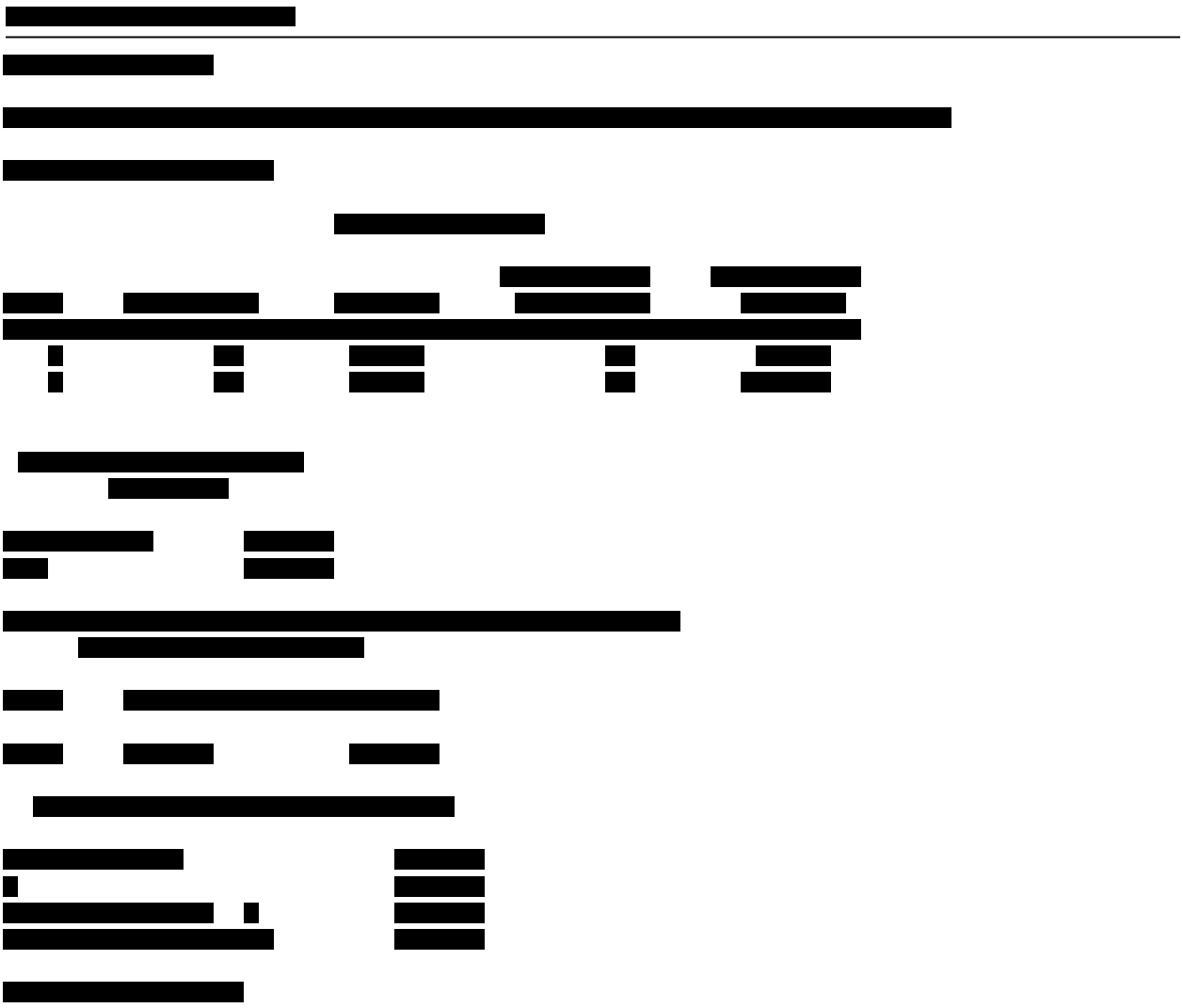


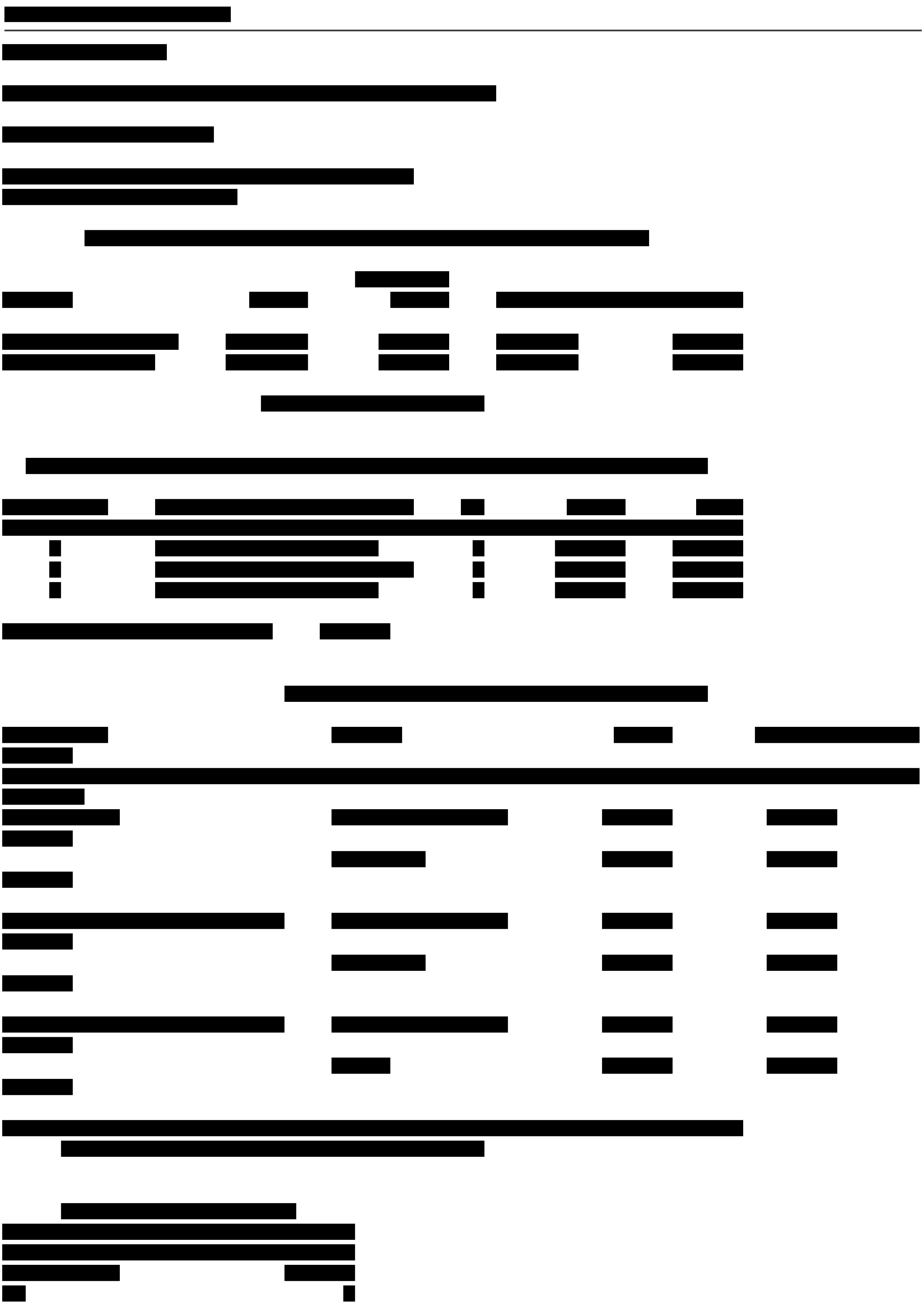








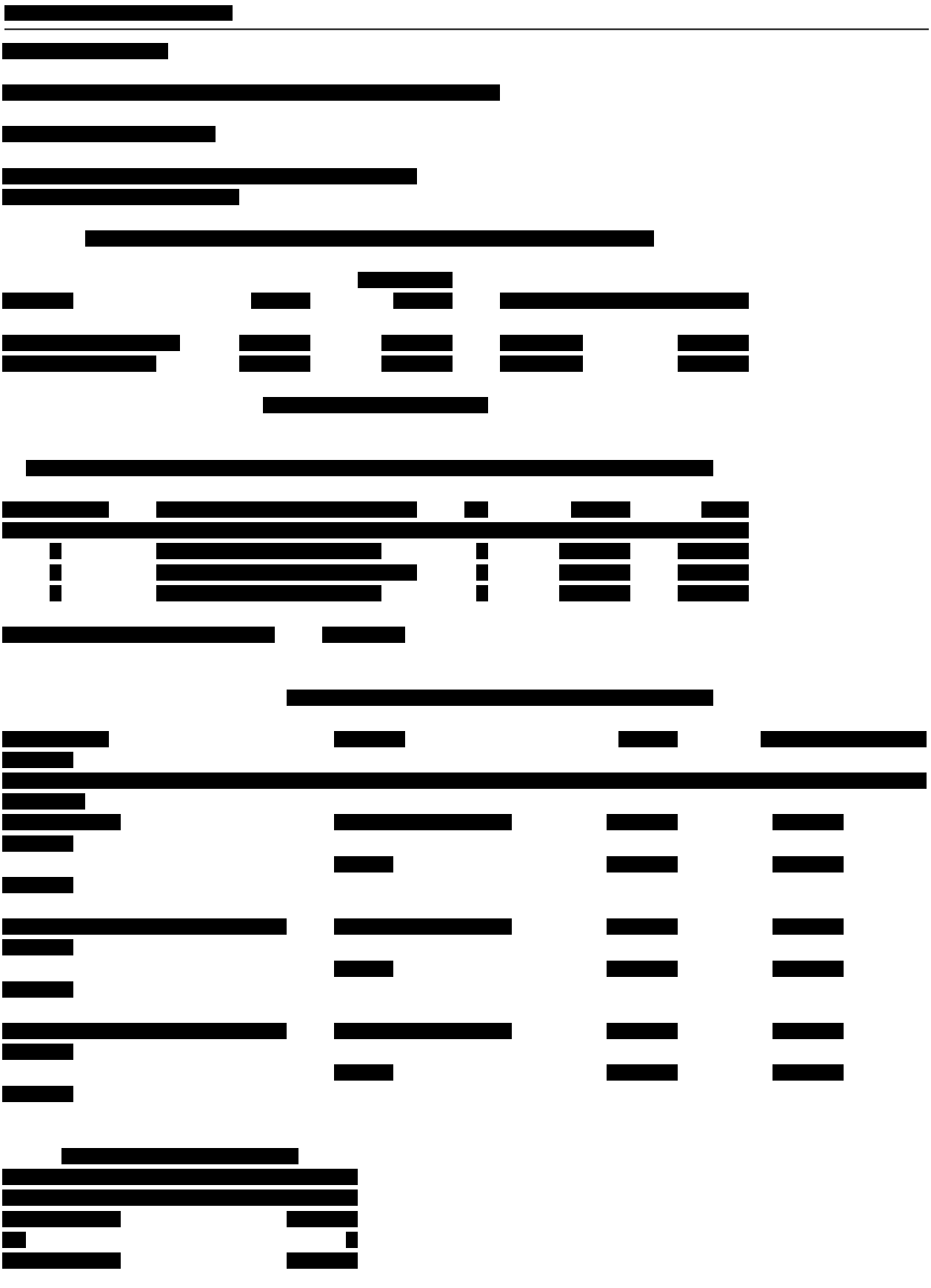


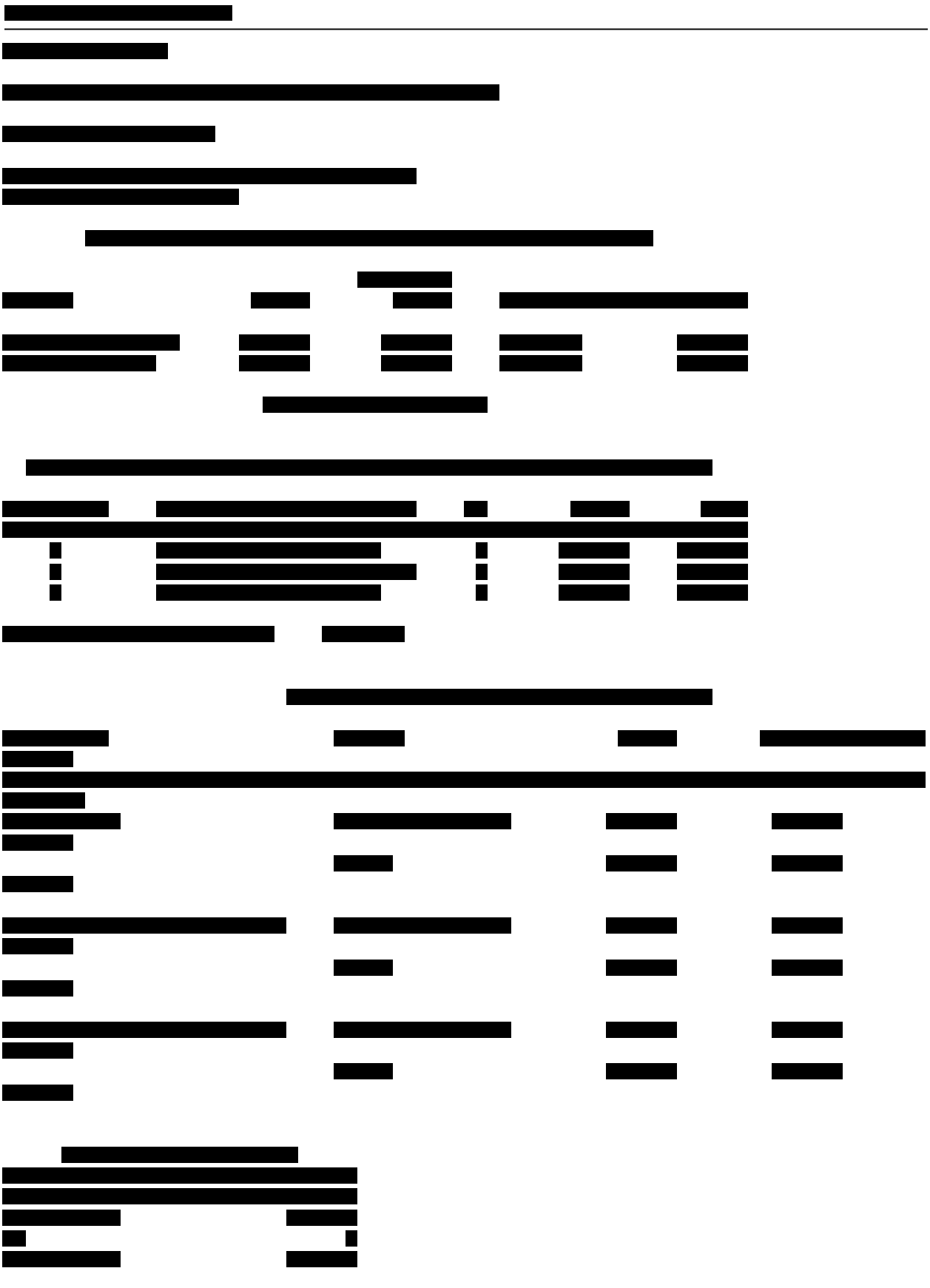


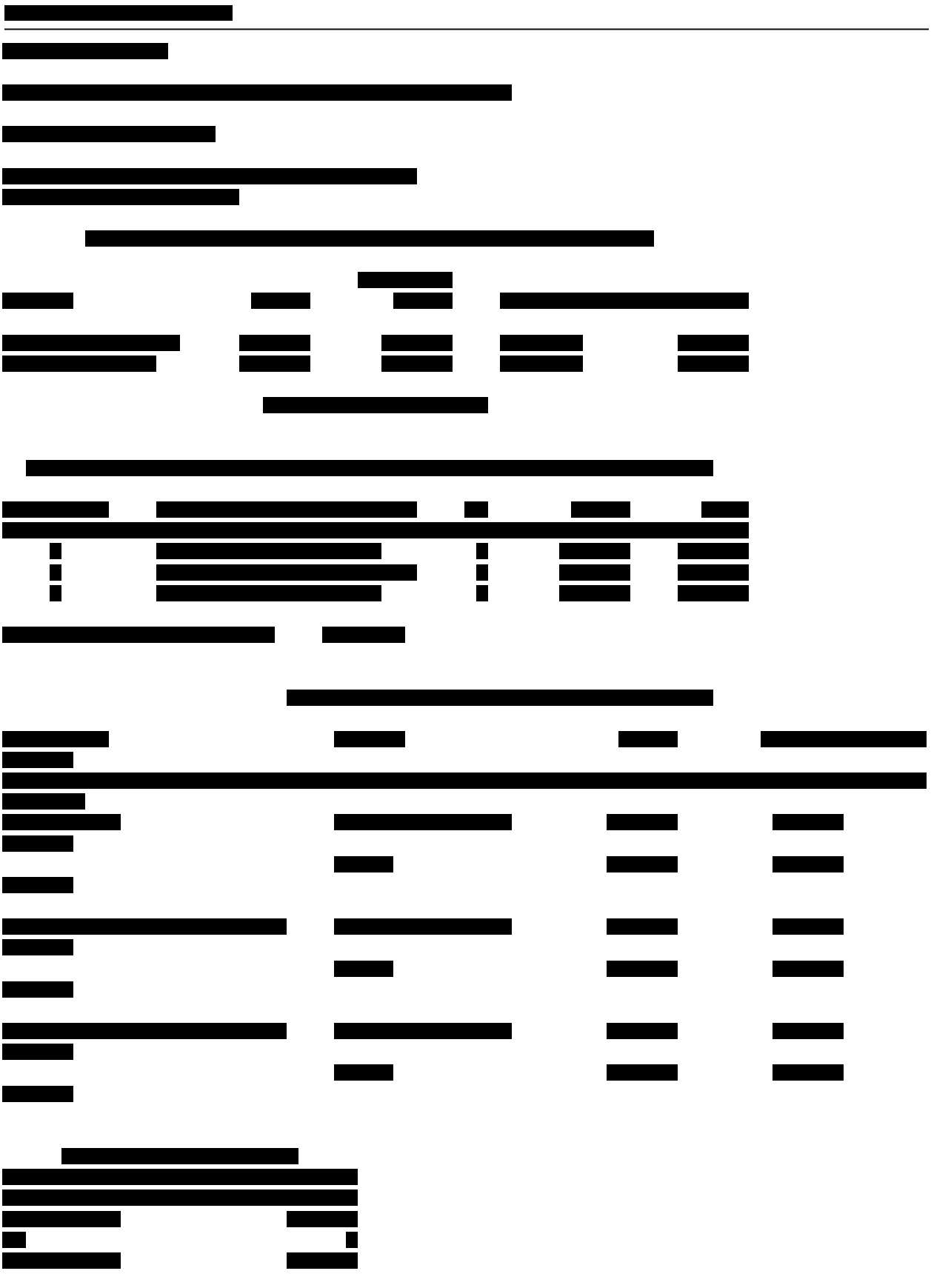
[redacted]

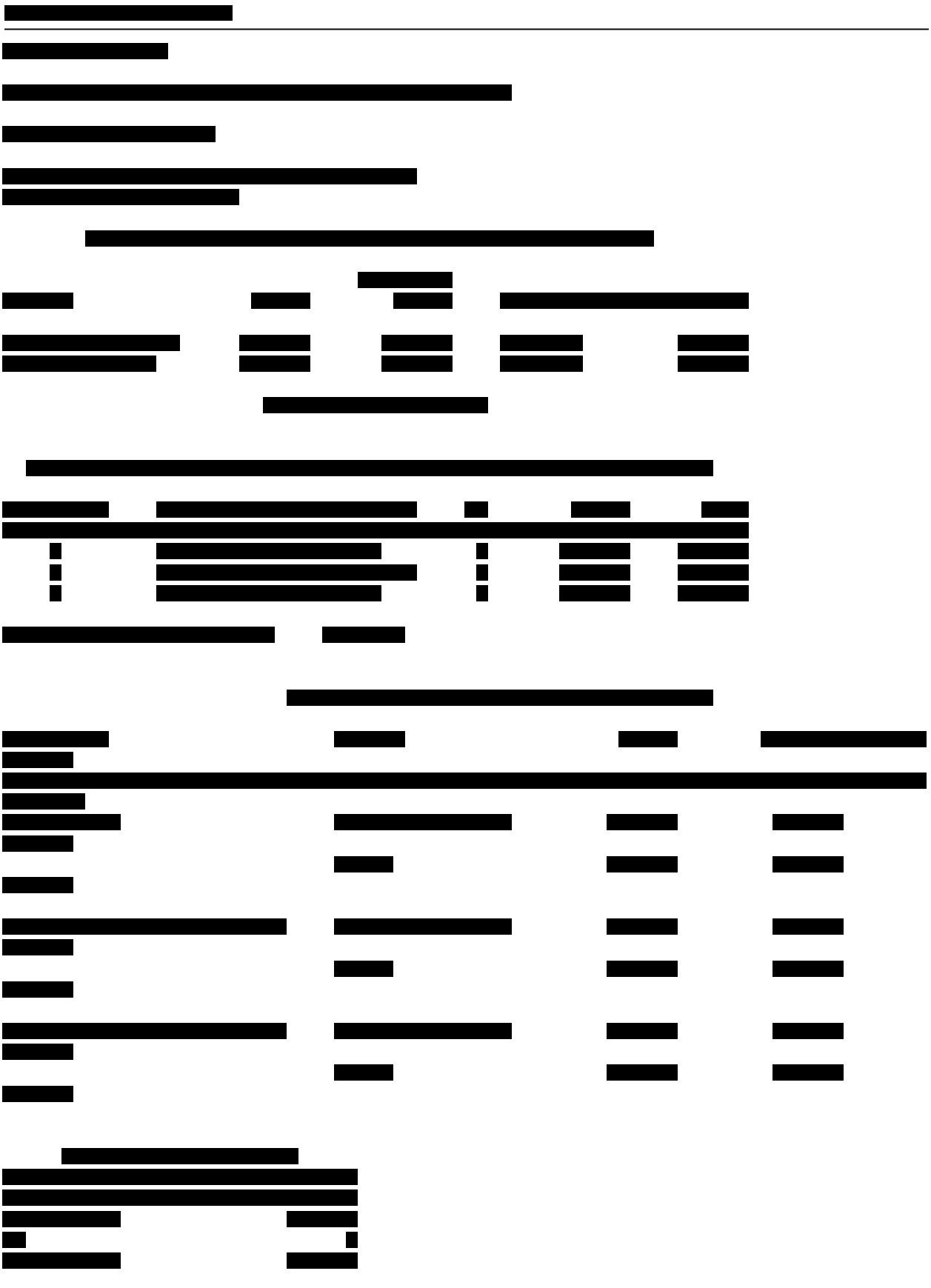
[redacted]

[redacted]









[redacted]

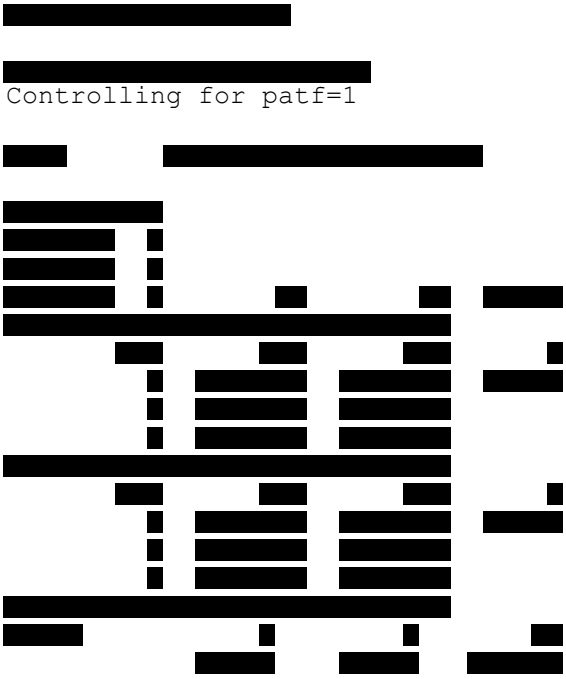
[redacted]

[redacted]

[redacted]

Controlling for patf=1

[redacted]



[redacted]