Statistical Analysis Plan

A randomized, placebo-controlled, double-blind, multi-center trial to assess efficacy and safety of octreotide subcutaneous depot (CAM2029) in patients with symptomatic polycystic liver disease

Trial Number:	**HS-20-677**
Indication:	**Polycystic liver disease**
Investigational Medicinal Product:	**CAM2029**
Development Phase:	**Phase 2/3 (Phase 2b in US)**
SAP version:	**Final Version 3**
Date:	**31-Mar-2025**
Sponsor:	**Camurus AB** **Ideon Science Park** **SE-223 70 LUND, Sweden**

STATISTICAL ANALYSIS PLAN APPROVAL

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VERSION HISTORY

This SAP for trial HS-20-677 is based on version 8 of the protocol, dated 29-Jan-2025.

SAP Version	Date	Change	Rationale	Protocol version
[redacted]				

LIST OF ABBREVIATIONS

ADPKD	Autosomal dominant polycystic kidney disease
[redacted]	[redacted]
ADPLD	Autosomal dominant polycystic liver disease
ADR	Adverse drug reaction
AE	Adverse event
[redacted]	[redacted]
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR(1)	First-order autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{ss}	Area under the plasma concentration-time curve at steady state
BLQ	Below the lower limit of quantification
cAMP	Cyclic adenosine monophosphate
$C_{av,ss}$	Average plasma concentration during a dosing interval at steady state
CDK-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	[redacted]
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EDC	Electronic data capture
ECG	Electrocardiogram
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End-of-treatment
ePRO	Electronic patient-reported outcome
FAS	Full analysis set

FCS	Fully conditional specification
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
htTLV	Height-adjusted total liver volume
htTKV	Height-adjusted total kidney volume
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
IMP	Investigational medicinal product
IR	Immediate release
IRB	Institutional Review Board
ITT	Intention-to-treat
LAR	Long-acting release
LLT	Lowest level term
LOCF	Last observation carried forward
LS	Least square
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effects model repeated measures
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
OC	Observed cases
PC1	Polycystin-1
PC2	Polycystin-2
PD	Pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PLD	Polycystic liver disease

PLD-I	Polycystic Liver Disease Impact
PLD-S	Polycystic Liver Disease Symptoms
PLD-Q	Polycystic Liver Disease Questionnaire
PPS	Per protocol analysis set
PQC	Product Quality Complaint
PRO	Patient-reported outcome
[redacted]	[redacted]
PT	Preferred term
Q1W	Once weekly
Q2W	Every 2 weeks
QTcF	QTc interval corrected by Fridericia's formula
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
[redacted]	[redacted]
SF-36	Short Form-36
[redacted]	[redacted]
SOC	System organ class
SRL	Somatostatin receptor ligand
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TLF	Table, Listing, and Figure
TLV	Total liver volume
[redacted]	[redacted]
US	United States
WHO-DD	World Health Organization Drug Dictionary

DEFINITION OF TERMS

CAM2029 Q1W	CAM2029 10 mg once weekly
CAM2029 Q2W	CAM2029 10 mg once every 2 weeks (weekly alternation with placebo)

CAM2029	The 2 CAM2029 treatment groups together
Placebo	Placebo once weekly
Overall	CAM2029 and Placebo together

1 STATISTICAL ANALYSIS PLAN STATEMENTS

Scope

This SAP will cover the planned analyses and reporting of the results from the double-blind treatment period of HS-20-677. A separate analysis plan will be written to cover the extension period following the double-blind period.

2 INTRODUCTION

The protocol for Trial HS-20-677 describes the general approach to analysis of data from the trial. This SAP provides additional details needed to complete such an analysis. Table, Listing, and Figure (TLF) shells are provided in a separate document.

This SAP will govern the efficacy, safety analysis, and descriptive summaries of PK data from this trial, see Section 1. The details of PK parameter derivations are outside the scope of this analysis plan and will be covered in a separate analysis plan, if applicable. The SAP may be modified until the time of database lock and treatment unblinding for the primary analysis. Any deviations from the analysis plan, including deviations made after treatment unblinding, will be documented as such in the trial report.

Changes to the protocol-planned analyses are described in Section 5.15.

This SAP is written based on version 8.0 of clinical trial protocol HS-20-677 (dated 29-Jan-2025).

2.1 Objectives, Endpoints, and Estimands

Table 1: Primary objective, endpoint and estimand

Primary Objective	Primary Endpoint / Estimand
• To evaluate the treatment effect of CAM2029 compared to placebo on liver volume in patients with PLD	**Endpoint:** Change from baseline to Week 53 in htTLV as determined by MRI volumetry **Estimand:** The primary estimand of interest is the mean change from baseline to Week 53 in htTLV comparing 2 doses of CAM2029 to placebo in patients with PLD, had no patients started treatment with alternative SRL or undergone any therapeutic intervention with the intention to reduce the liver size, and is defined by the following attributes: 1. Treatment condition: The primary treatment condition of interest is the average effect of: • The CAM2029 treatment (10 mg once weekly and 10 mg every 2 weeks) vs placebo treatment Thereafter, the treatment conditions of interest are the effects of: • CAM2029 10 mg once weekly vs placebo • CAM2029 10 mg every 2 weeks vs placebo 2. Target population: The population targeted by the clinical question is defined as patients in the ITT analysis set as defined by the inclusion/exclusion criteria in the trial protocol. 3. Variable (endpoint): The variable addressing the primary clinical question is change from baseline in htTLV as assessed at Week 53. 4. Handling of intercurrent events: Intercurrent events will be handled through a combination of a treatment policy strategy and a hypothetical strategy depending on other treatment received and therapeutic interventions conducted while still in the trial:

Primary Objective	Primary Endpoint / Estimand
	• IMP treatment discontinuation: Patients who discontinue treatment with IMP and do not receive another SRL or have any therapeutic interventions with the intension to reduce the liver size while still in the trial will be analyzed by the treatment policy strategy, i.e., observations collected after IMP discontinuation will be included in the analysis as they were collected. For patients who discontinue treatment with IMP and start receiving another SRL or have any therapeutic intervention with the intension to reduce the liver size while still in the trial, only observations collected prior to the start of the SRL and the therapeutic intervention will be included in the analyses. Observations collected after the start of the SRL and the therapeutic intervention will be handled using the method described below. • Use of another SRL (see Appendix 12): Patients who receive an SRL other than the trial IMP while still in the trial, will be handled according to a hypothetical strategy. That is, any measurements of htTLV following the start of any other SRL administration will be set to missing and not used in the analysis. This hypothetical strategy is motivated by the fact that no approved alternative SRL treatment for PLD is available in most countries. • Therapeutic interventions: Patients undergoing therapeutic intervention with the intention to reduce the liver size while still in the trial will be handled according to a hypothetical strategy. That is, measurements of htTLV following this intercurrent event will be set to missing and not used in the analysis. This strategy is motivated by the fact that such interventions may directly impact the primary endpoint without being related to the effect of the IMP. • Missing values: If the htTLV cannot be determined at Week 53, either due to start of another SRL treatment or after a therapeutic intervention with the intention to reduce the liver size after IMP discontinuation or values are missing for other reasons, missing values will be imputed using the MI method described in the Section 5.3.1 and Section 5.9.2.2. 5. Population-level summary for comparison between treatment conditions: Mean change from baseline to Week 53 in htTLV

Table 2: Key Secondary objective, endpoint and estimand

Key Secondary Objective	Key Secondary Endpoint / Estimand
• To evaluate the treatment effect of CAM2029 compared to placebo on patient-reported PLD-related symptoms	**Endpoint:** Change from baseline to Week 53 in the PLD-S measure score [redacted]

Table 3: Secondary objectives, endpoints and estimands

Secondary Objective	Secondary Endpoint / Estimand
• To evaluate the treatment effect of CAM2029 on liver volume over time in patients with PLD	**Endpoint:** Change from baseline in htTLV as determined by MRI volumetry [redacted]
• To evaluate the treatment effect of CAM2029 on patient-reported PLD-related symptoms over time	**Endpoint:** Change from baseline in the PLD-S measure score [redacted]

Secondary Objective	Secondary Endpoint / Estimand
	[redacted]
• To evaluate the treatment effect of CAM2029 over time on kidney volume in patients with presence of kidney cysts	**Endpoint:** Change from baseline in htTKV as measured by MRI volumetry [redacted]

Secondary Objective	Secondary Endpoint / Estimand
	[redacted]
• To evaluate treatment effect of CAM2029 over time on total liver cyst volume	**Endpoint:** Change from baseline in total liver cyst volume determined by MRI volumetry [redacted]

Secondary Objective	Secondary Endpoint / Estimand
	[redacted]
• To evaluate the treatment effect of CAM2029 over time on renal function in patients with presence of kidney cysts	**Endpoint:** Change from baseline in eGFR, assessed by the CKD-EPI cystatin C equation using serum concentrations of creatinine and cystatin C [redacted]
• To evaluate the treatment effect of CAM2029 over time on patient-reported PLD-related impact on functioning and well-being	**Endpoint:** Change from baseline in the PLD-I measure score [redacted]
• To evaluate the treatment effect of CAM2029 over time on PLD-related symptoms	**Endpoints:** • Change from baseline in the CGI-S score • Change from baseline in the PGI-S score • Change from baseline in the PGI-C score [redacted]

Secondary Objective	Secondary Endpoint / Estimand
• To evaluate the treatment effect of CAM2029 over time on functioning and well-being	[redacted]
• To evaluate the treatment effect of CAM2029 over time on PLD-related symptoms	**Endpoint:** Change from baseline in the PLD-Q score [redacted]
• To evaluate the safety and tolerability of CAM2029	**Endpoints:** • Incidence of AEs • Changes from baseline in laboratory values, vital signs and ECG readings
• To assess the PK of octreotide after administration of CAM2029	**Endpoint:** Octreotide plasma concentrations over time

Table 4: Exploratory objectives, and endpoints

Exploratory Objectives	Exploratory Endpoints
[redacted]	

[redacted]

2.2 Trial Design

This is a Phase 2/3 (Phase 2b in the US), randomized, placebo-controlled, double-blind, multi-center trial designed to evaluate the efficacy and safety of 2 treatment regimens of CAM2029 versus placebo in patients with PLD. Approximately 69 patients will be randomized in the trial.

The trial consists of an up to 12-week Screening Period followed by a 52-week (12-month) Double-Blind Treatment Period for which patients will be randomized in a 1:1:1 ratio to 1 of the 3 treatment arms:

- Arm 1: CAM2029 10 mg once weekly
- Arm 2: CAM2029 10 mg every 2 weeks (weekly alternation with placebo)
- Arm 3: Placebo once weekly

Following completion of the Double-Blind Treatment Period, all patients will continue to a 120-week (30-month), open-label, single-arm, extension period with CAM2029 10 mg once weekly, followed by an 8-week safety follow-up period. The estimated duration of the trial for each patient is approximately 47 months.

A primary endpoint analysis will be performed when the last patient has completed the Double-Blind Treatment Period (Week 53).

An overview of the trial design is shown in Figure 1.

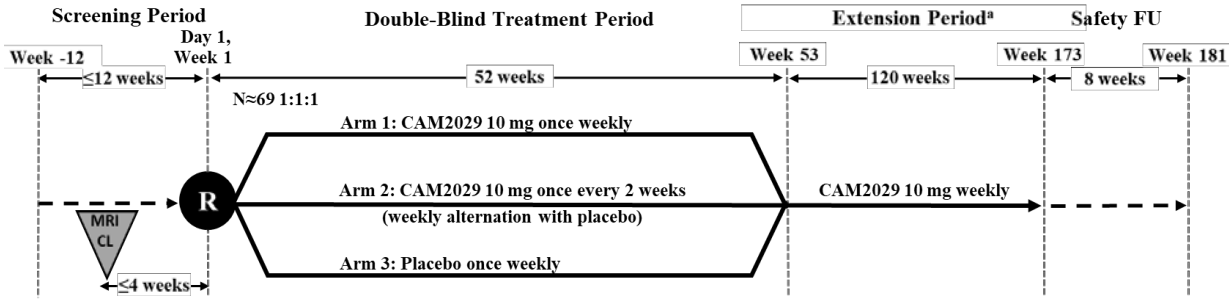


Figure 1: Trial design

CL: clinical laboratory sampling; FU: follow-up; MRI: magnetic resonance imaging; N: number of patients; R: randomization

a Dose reduction to CAM2029 10 mg every 2 weeks will be allowed in the Extension Period.

The trial population is comprised of adult patients (≥18 years) who are diagnosed with PLD associated with ADPKD or isolated as in ADPLD, and who meet all the inclusion criteria and none of the exclusion criteria specified in Section 5 of the clinical trial protocol.

3 STATISTICAL HYPOTHESES

The primary objective is to assess superiority of treatment with CAM2029 compared to placebo on liver volume in patients with PLD.

The key secondary objective is to assess superiority of treatment with CAM2029 compared to placebo on patient-reported PLD-related symptoms.

In the analysis of the primary and key secondary efficacy endpoints, the primary comparison will be between the average effect of the 2 CAM2029 doses compared to placebo. In addition, the 2 doses of CAM2029 will be compared with placebo separately.

3.1 Multiplicity Adjustment

Two doses of CAM2029 are analyzed in the trial. To protect the overall significance level, the following closed order testing procedure will be used:

1. The effect of the combined CAM2029 treatment groups compared to placebo on change in htTLV at Week 53
2. The effect of treatment with CAM2029 10 mg given once weekly compared to placebo on change in htTLV at Week 53
3. The effect of treatment with CAM2029 10 mg given every 2 weeks compared to placebo on change in htTLV at Week 53

Each test will be performed on the 5% significance level starting with the first test in the list and stopping the testing procedure at the first test for which the p-value is larger than 0.05.

4 ANALYSIS SETS

All screened patients will be accounted for in the clinical trial report.

The decisions regarding inclusion/exclusion of patients from the trial analysis sets will be documented in the analysis set definition document before breaking the randomization code.

The following analysis sets are defined in this trial:

4.1 Screened Set

The screened Set will include every patient who has signed informed consent form. The screened Set will be used for summaries of disposition and the associated listing.

4.2 Intention-to-treat Analysis Set

The ITT analysis set will consist of all patients who were randomized to a treatment arm in double-blind treatment period. Analyses based on this population will group patients according to the treatment they were randomized to receive, regardless of actual treatment received.

The efficacy analyses will be primarily based on the ITT analysis set.

4.3 Full Analysis Set

The FAS comprises all patients in the ITT analysis set who were administered at least 1 dose of the IMP. Analyses based on this population will group patients according to the treatment they were randomized to receive, regardless of actual treatment received.

The primary and key secondary efficacy analyses will also be performed based on FAS. If ITT = FAS, the analysis will not be repeated for FAS.

4.4 Per Protocol Analysis Set

The PPS is defined as all patients in the ITT analysis set with no important (major) protocol deviations that would have an impact on the efficacy assessment or any other criterion, as deemed appropriate.

Analyses based on PPS will be of supportive purpose and limited to the primary and key secondary endpoints. Patients will be analyzed according to their actual treatment received.

4.5 Important Protocol Deviations Leading to Exclusion from the Per Protocol Analysis Set

Protocol deviations are defined as any change, divergence, or departure from the trial design or procedures defined in the trial protocol. Important (or major) protocol deviations are protocol deviations that may significantly impact the correctness, accuracy, and/or reliability of the trial data, or that may significantly affect a patient's rights, safety, or well-being.

The criteria to exclude patients from the PPS will be selected based on a blinded review of the data and finalized prior to unblinding of the trial for the primary analysis.

4.5.1 Reporting of Protocol Deviations

All protocol deviations will be periodically reviewed and classified (major or minor) as described in the clinical monitoring plan prior the database lock for the Double-blind Treatment Period. Protocol deviations classified as important (or major) may lead to exclusion from analysis sets, see Section 4.

Major protocol deviations will be summarized by category. All protocol deviations will be listed.

4.6 Pharmacokinetic Analysis Set

The PK analysis set comprises all patients who were administered at least 1 dose of CAM2029 and for whom at least 1 plasma octreotide concentration after the first CAM2029 dose is available.

The PK analysis set will be used for the analyses of PK data.

4.7 Safety Analysis Sets

The SAF comprises all patients who were administered at least one dose of IMP during the double-blind treatment period. Analyses based on this population will group patients according to the actual treatment the patients received.

The safety analyses will be based on the SAF.

5 STATISTICAL ANALYSES

5.1 General Considerations

Three types of data display will be produced for this trial: summary tables, figures, and data listings (also referred to as TFLs), as specified in the sections below.

Unless stated otherwise, data listings will be produced for all recorded data. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Data listings will simply list the data recorded on the eCRF/vendor data or derived for each patient. Data listings will be ordered by treatment, patient number, and time of assessment if no further preference/hierarchy is specified.

Summary tables will display summary statistics calculated for each of the treatment groups, i.e. CAM2029 Q1W, CAM2029 Q2W, CAM2029, Placebo, and Overall, unless described otherwise in the following sections.

Continuous variables will be summarized with the number of non-missing values, mean, standard deviation, median, minimum, maximum, and quartiles. Categorical variables will be summarized with the number and percentages of patients in each category. Percentages of patients in each of the possible categories will be calculated from the number of patients in the corresponding analysis set, unless stated otherwise in tables, figures, and listings (TFLs). Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

Safety parameters will be presented descriptively.

All data processing, summarization and analyses will be performed using SAS Version 9.4 (or later) of the SAS® statistical software package.

Therapeutic interventions with the intention to reduce the liver size included in the estimand definition, will be defined prior to DBL.

5.1.1 Data Sources

Data are recorded on eCRFs. Central laboratory data (including safety, PK, [redacted], and immunogenicity), centralized imaging readings, ePRO, eCOA, central ECG, and other imaging data results will be provided via electronic data transfers.

Section 9 of the clinical trial protocol provides additional details regarding data recording and handling.

5.2 Time Points and Visit Windows

5.2.1 Definition of Baseline

Baseline is defined as the last available observed value of the parameter of interest prior to the first administration of IMP during the double-blind treatment period (this includes unscheduled visits). For 12-lead ECG, baseline is defined as the average of the last non-missing triplicate measurements prior to the first administration of IMP. If there are less than 3 measurements, the available measurements will be used.

Change from baseline is calculated as post-baseline value minus the baseline value. Percentage change from baseline is calculated as follows: (post-baseline result – baseline result) / baseline result*100.

5.2.2 Calculation of Trial Day

For any events/assessments on or after the first IMP administration, trial day is calculated as: event/assessment date – date of first administration of IMP + 1. As such, the first IMP administration date during the treatment period is trial day 1.

For any events/assessments before the first administration date, trial day is calculated as event/assessment date – date of first administration of IMP.

5.2.3 Analysis Visit Window

5.3 Handling of Missing Data

5.3.1 Handling of Missing Efficacy Data

The missing primary and key secondary efficacy data up to Week 53 will be imputed using MI. Imputation will be performed using an FCS regression method.

The procedure for the change from baseline is htTLV is described below.

A regression model will be fitted to the htTLV values at Week 13. The model will include effects of baseline htTLV as a covariate. The estimated parameters and their variances will be used to impute missing htTLV values at Week 13.

Missing htTLV values at Week 25 will be imputed in the same way as Week 13. The model will include effects of baseline htTLV as a covariate together with the htTLV value at Week 13 as a covariate. The estimated parameters and their variances will be used to impute missing values at Week 25.

The procedure will be repeated for missing htTLV values at Week 53 with the modification that htTLV values from the preceding 2 visits will be included as covariates in addition to the baseline htTLV.

Detailed procedures for handling of missing values are included in the sections describing the individual analyses.

5.3.2 Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. AE imputations for missing severity or relationship are given in Section 5.10.1. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.3.3 Handling of Partial and Missing Dates for Adverse Events, Prior/Concomitant Medication, and IMP Administration

Partial dates may be entered in the eCRF for adverse events and prior and concomitant medications. Dates from these forms will be reported in listings as collected and imputed. Every effort will be made to query missing dates.

AEs that cannot be definitely determined as occurring prior to IMP administration will be counted as TEAEs unless either the partial start date or a partial or complete end date indicates the AE as occurring prior to treatment. Partial dates entered in the AE form will be imputed for the purposes of determining whether the record is a TEAE or not based on the following:

- AE onset dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the month and year of first dosing of IMP, in which case the date will be imputed using the date of first dosing of IMP.
- AE onset dates with missing day and month will be assumed to occur on the first day of the non-missing year (i.e., 01-Jan-YYYY), except for AEs occurring in the year of first

dosing of the IMP, in which case the date will be imputed using the date of the first dosing of IMP.

- Partial or missing AE resolution dates will not be imputed.

Partial dates entered in the Prior and Concomitant Medications form will be imputed for the purposes of determining whether the record is a concomitant or prior medication based on the following:

- Medications that are not ongoing and have a medication stop date with a missing day and non-missing month will be assumed to occur on the last day of the non-missing month.
- Medications that are not ongoing and have a medication stop date with missing day and month will be assumed to occur on the last day of the non-missing year (i.e., 31-Dec-YYYY).
- Partial or missing CM start dates will not be imputed.
- If both start and end/stop dates are missing, then the medication will be classified as concomitant.

If the imputed medication end date is later than the date of last visit, the last visit date will be used as the end date.

5.3.4 Handling of Plasma/Blood Serum Concentrations that are Below the Lower Limit of Quantification

Plasma/blood/serum concentrations that are BLQ will be handled as follows for descriptive statistics:

- Values that are BLQ will be set to the lower limit of quantification for the calculation of summary statistics.

5.4 Treatment Labels

Table 6: Treatment labels for the statistical output

Period	Labels Used in Tables	Order in Table
Double-blind treatment period	CAM2029 Q1W	1
Double-blind treatment period	CAM2029 Q2W	2
Double-blind treatment period	CAM2029	3
Double-blind treatment period	Placebo	4
Double-blind treatment period	Overall	5

5.5 Trial Population

5.5.1 Demographics and Baseline Characteristics

Patient characteristics defined below will be presented in summary tables and data listings for patients in the ITT analysis set. The presentations will be for the following treatment groups:

CAM2029 Q1W, CAM2029 Q2W, CAM2029, Placebo, and Overall. No formal statistical comparisons will be performed.

Demographics:

- Age (years)
- Age group: <65, ≥ 65 years
- Sex
- Childbearing potential (Yes/No. If No, alternatives will be presented))
- Menopausal status
- Race
- Ethnicity

Baseline characteristics:

- Height (cm)
- Weight (kg)
- BMI (kg/m2)
- htTLV (mL/m)
- PLD-S measure score
- eGFR (mL/min/1.73m^2)
- Alkaline Phosphatase (IU/L)
- Isolated ADPLD
- PLD associated with ADPKD

5.5.2 Medical History

Medical history will be coded using MedDRA version 25.0 (or a later version, if updated during the trial or in relation to DBL and agreed with the Sponsor). Medical history will be summarized by SOC and PT using frequencies and proportions.

Disease characteristics will also be listed and presented descriptively.

5.6 Patient Disposition

Patient disposition will be summarized as the number and percentage of patients screened, failed screening, randomized, completed the treatment during the double-blind treatment period, discontinued IMP during the double-blind treatment (including reason for IMP discontinuation), continued treatment in the extension period, completed participation in the double-blind treatment period, withdrawal from the trial (including reason for withdrawal), and analysis sets.

The disposition and population inclusion data mentioned above will be listed for all patients. The reasons for being excluded from the analysis sets will also be provided in the listings.

In addition, a separate disposition table summarizing the inclusion/exclusion criteria not met for screen failures will be provided.

5.7 Prior and Concomitant Medications and Non-Pharmacological Procedures

Prior and concomitant medications will be coded using the WHO DD version B3 Global March 2022 (or a later version, if updated during the trial or in relation to DBL and agreed with the Sponsor).

Prior medications are defined as any medications taken and stopped prior to the start of the IMP administration.

Concomitant medications in the treatment period are defined as medications with a start date on or after the first IMP administration or medications with a start date prior to first IMP administration but ongoing or with stop dates on or after first IMP administration.

The following concomitant medication summaries will be produced by WHO-DD ATC classification second level (alphabetically), ATC classification forth level, and preferred base name with the number and percent of patients by treatment groups and active treatment groups pooled together, presented in double-blind treatment period:

- Concomitant medications ongoing at the first IMP administration or started on or after the first IMP administration
- Concomitant medications with start date after the first IMP administration

The tables will display the number and percentages of patients who reported at least one prior or concomitant medication in each ATC level. Within each ATC level, the tables will display the number and percentages of patients reporting at least one medication as designated by the preferred base name. The outputs will be presented by descending frequency across all patients for a given ATC level and preferred base name. Patients may have more than 1 medication per ATC classification/preferred base name. At each level of summarization, a patient will be counted once if he/she reported one or more medications per ATC classification/preferred base name.

A listing of prior and concomitant medications will also be provided.

Treatments of PLD or its related symptoms, including prophylactic treatments, will be listed and summarized descriptively.

Prior and concomitant non-pharmacological procedures will be coded using MedDRA version 25.0 (or a later version if updated during the trial or in relation to DBL and agreed with the Sponsor), associating LLTs with PTs and SOC by the primary hierarchy.

Prior procedures and concomitant procedures in the treatment period will be defined using similar methods as for prior and concomitant medication above.

Prior and concomitant non-pharmacological procedures will be summarized by SOC, and PT with the number and percent of patients.

A listing of prior and concomitant non-pharmacological procedures will also be provided.

5.8 Extent of Exposure and Treatment Compliance

5.8.1 Extent of Exposure

Exposure to CAM2029 or placebo will be summarized using the following parameters based on the data collected in the EDC system in the doble-blind treatment period:

- Treatment duration (in weeks), calculated as the number of weeks the patient received IMP: (date of last dose of IMP within each trial period - date of first dose of IMP + 5 half-lives (i.e., 53 days))/7.
- Total number of injections taken, as documented in the patient diary and the eCRF.

The duration of exposure in weeks will be summarized by treatment arm (including the combined active treatment groups) and overall using descriptive statistics for the safety analysis set. The number and percentage of patients with a cumulative duration of exposure will be presented for the following periods: ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥24 weeks, ≥36 weeks, and ≥52 weeks.

5.8.2 Treatment Compliance

Compliance to CAM2029 or placebo will be summarized using the following parameters based on the data collected in the EDC system in the double-blind treatment period:

- Percent compliance, calculated as:
  (Total number of injections taken)/(Total number of planned injections) × 100

  where the total number of planned injections is calculated as the number of weeks that the patient has been treated from Day 1 or the number of weeks from Day 1 to the last completed planned visit, whichever is the last.
- Percent compliance categories, <80%, ≥80 and <120%, ≥120%

The above parameters will be summarized for each treatment group, the combined active treatment groups, and overall (i.e., all treatment groups pooled together). A listing of the exposure and compliance parameters will also be provided. Patient diary data will also be present in listings.

5.9 Efficacy Endpoints and Analyses

All efficacy data will be included in data listings and summary tables and/or figures. The efficacy analyses of the double-blind treatment period will be performed using the ITT, FAS, and PPS, as described in the following sections. The combined active treatment groups will be summarized for efficacy analyses during the double-blind treatment period. Patients will be analyzed according to the treatment assigned at randomization except for summaries based on the PPS, where patients will be analyzed according to the actual treatment given.

Kidney-related variables, i.e., total kidney volume and eGFR, will also be analyzed for patients with presence of kidney cysts and summarized by treatment arm, combined active treatment groups, and overall.

5.9.1 Multiple Testing Procedure

See Section 3.1.

5.9.2 Primary Efficacy Objective, Endpoint, and Estimand Analysis

The primary objective is to evaluate the treatment effect of CAM2029 compared to placebo on liver volume in patients with PLD.

The estimand for the primary objective is defined by the attributes described in Table 1.

The analysis will be primarily performed on the ITT analysis set.

5.9.2.1 Definition of the Primary Endpoint

The primary efficacy endpoint is defined as the change from baseline to Week 53 in htTLV as determined by MRI volumetry. Depending on the shape of the distribution of htTLV, data may be logarithm-transformed prior to analysis. After analysis of log-transformed data, the estimated parameters will be transformed back to the original scale using the exponential function, thus producing estimated geometric means and estimated ratio of means which will be presented together with 95% CIs.

5.9.2.2 Main Analytical Approach

The combined estimand is defined in Table 1 and incorporates two main types of events that influence how the treatment effects are estimated, i.e. initiation of another SRL or therapeutic intervention with the intention to reduce the liver size and permanent discontinuation of IMP.

Missing values will be imputed using the MI method described in the Section 5.3.1. Missing Week 53 data will be imputed using MI assuming that data are missing at random within the groups used for imputation.

[redacted]

For each of the imputed datasets, the primary efficacy endpoint will be analyzed using an ANCOVA model with fixed factor for treatment and baseline htTLV as covariate, within the

framework of a MI method. The main comparison will be between the average effect of the 2 CAM2029 doses compared to placebo (i.e., the contrast for the treatment difference is (0.5 0.5 0) – (0 0 1) where the 2 CAM2029 doses are given by the first two terms and placebo by the last). Additionally, each of the doses of CAM2029 will be compared with placebo separately as described in Section 3.1. For SAS code, see Appendix 1.

The estimated difference in mean change from baseline (average effect of combined CAM2029 – placebo) will be derived together with the associated standard error. The estimates and the standard errors from the 100 analyses will be combined to one estimate and associated standard error in PROC MIANALYZE using Rubin's rule. The resulting p-value will be reported. The combined estimated mean difference in change from baseline and associated 95% CI will also be reported.

Descriptive summary statistics of observed values and mean change from baseline to Week 53 in htTLV will also be presented by treatment groups.

5.9.2.3 Sensitivity Analyses

Tipping Point

If a significant difference can be detected from the primary analysis, a tipping point analysis (4) will be performed to investigate the robustness of departures from the MAR assumption in the MI model by applying a specified sequence of shift parameters that modify the imputed htTLV values [redacted]

Last Observation Carried Forward (LOCF)

The primary endpoint will be analyzed using the same ANCOVA model as described above for the primary analysis, but missing data will be imputed using last observed values post-baseline.

Mixed Model Repeated Measures (MMRM)

Analysis of Covariance (ANCOVA), Observed Cases (OC)

Similar to the primary efficacy analysis above, the primary endpoint will be analyzed using the same ANCOVA model with fixed factor for treatment and baseline htTLV as a covariate based on OC without imputation or handling of intercurrent events. The analysis will be performed on the ITT analysis set.

5.9.2.4 Supplementary Analyses

5.9.3 Key Secondary Efficacy Endpoint and Estimand

The estimand definitions applicable to secondary objectives are described in Table 2.

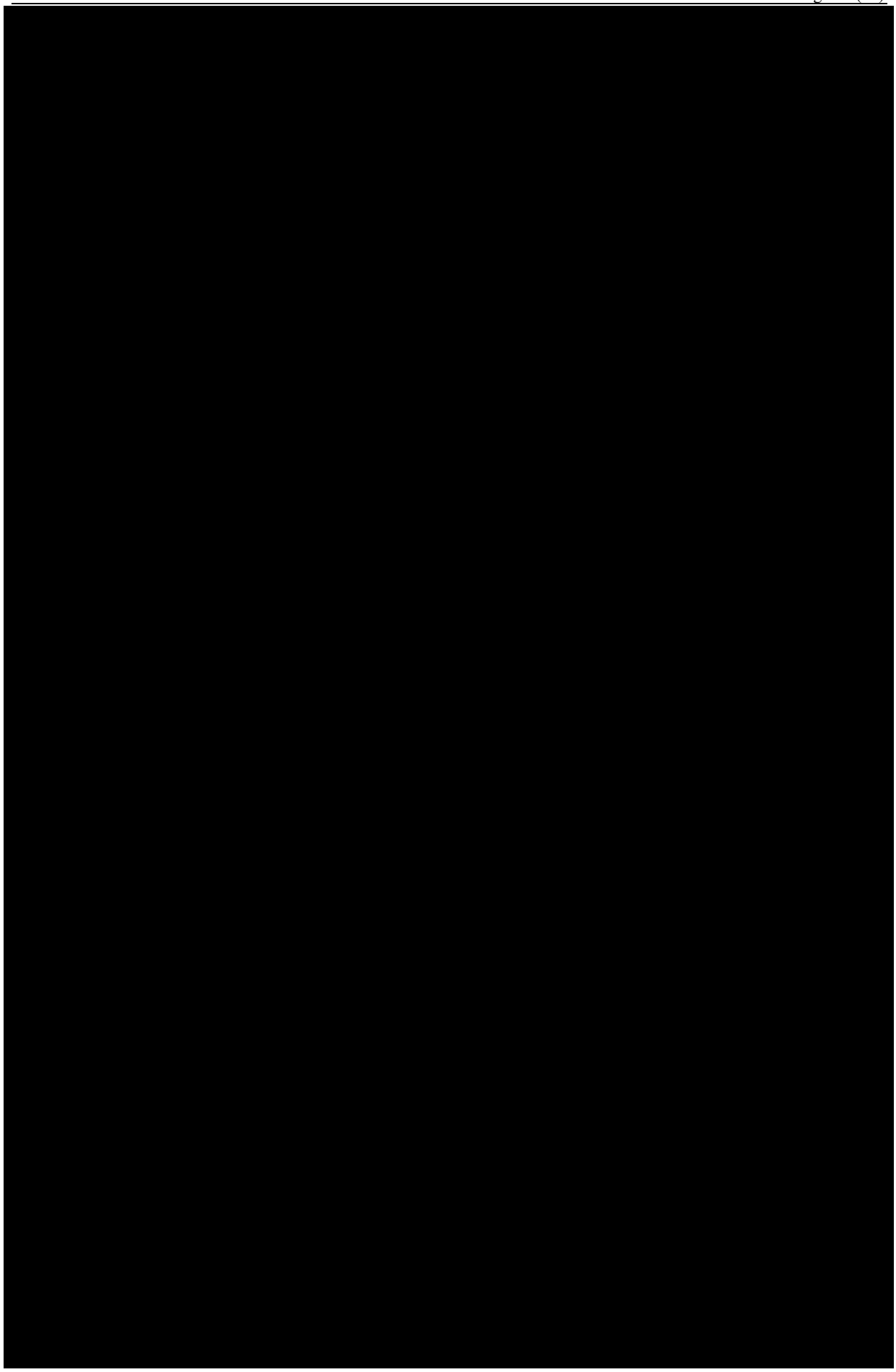
The PLD-S is a PRO currently under development to assess patient reported symptoms of PLD. [redacted]

The key secondary efficacy endpoint is change from baseline to Week 53 in the PLD-S measure score and this endpoint will be analyzed with the same methods as for the primary endpoint. In the analysis of the key secondary efficacy endpoint, the main comparison will be between the average effect of the 2 CAM2029 doses compared to placebo. In addition, the 2 doses of CAM2029 will be compared with placebo separately as described in Section 3.1.

5.9.4 Secondary Efficacy Endpoints and Estimands Analysis

The estimand and endpoint definitions applicable to secondary objectives are described in Table 3.

[redacted]

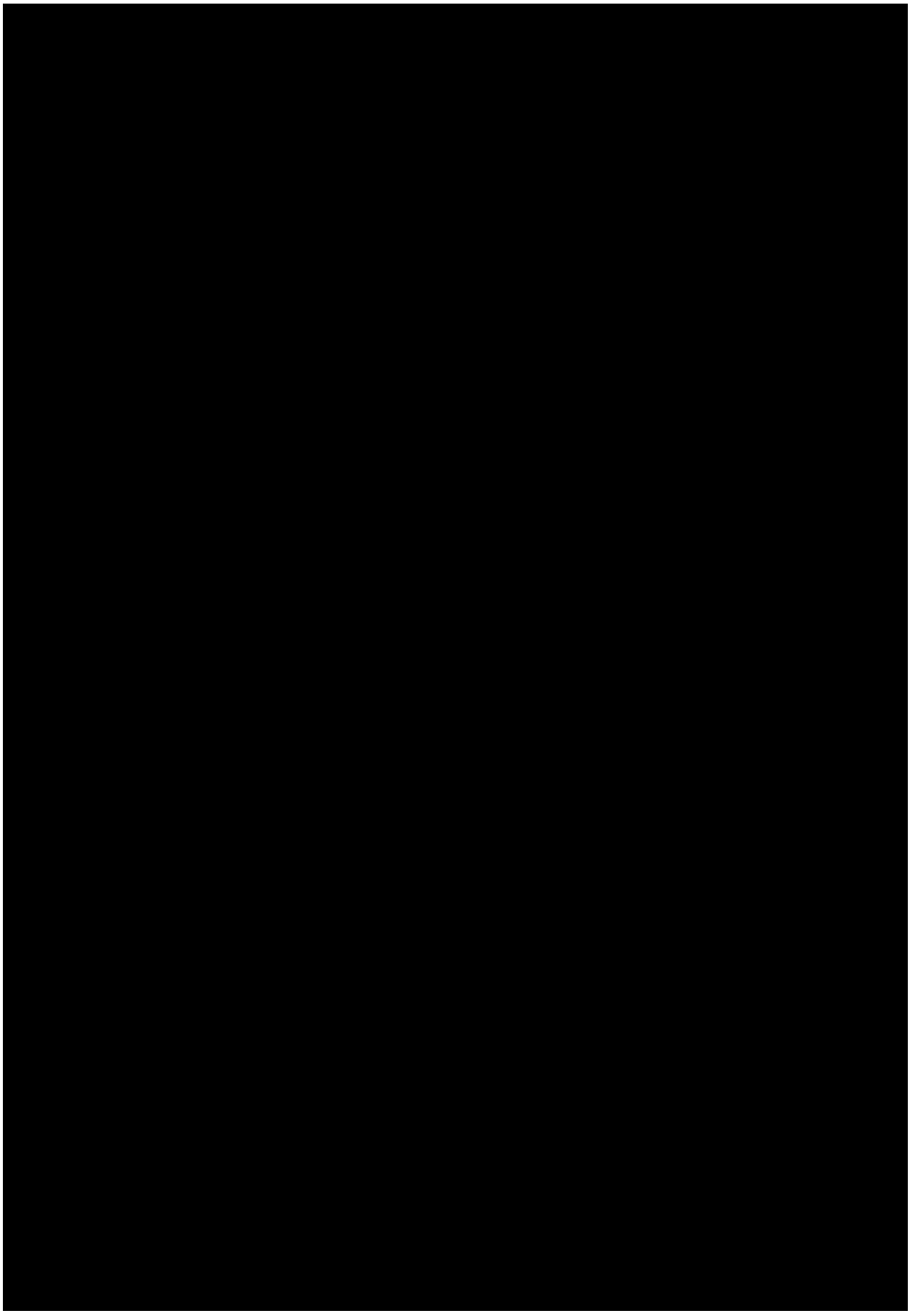


[redacted]

5.9.5 Exploratory Efficacy Endpoint(s) and Estimands Analysis

The following exploratory efficacy endpoints will be analyzed:

[redacted]



[redacted]

5.9.6 Subgroup Efficacy Analyses

Primary endpoint and key secondary endpoint data from subgroups of patients in the ITT will be analyzed as specified below. These analyses will comprise descriptive summaries; the goal will be to identify signals of additional effects that the primary analysis does not consider. Such analyses will be considered exploratory and will not involve hypothesis testing.

Prespecified subgroup analyses will be conducted for:

- Age [redacted]
- Sex (Male, Female)

[redacted]

5.10 Safety Endpoints and Analyses

Safety analyses will be performed for the treatment period based on the safety analysis set (SAF).

AEs starting in the double-blind period and ongoing at the first dose in the extension period will be assigned to the double-blind period and not to the extension period. This is to avoid counting the same AE twice.

5.10.1 Adverse Events

AEs will be coded using MedDRA version 25.0 (or higher version if updated during the trial or in relation to DBL and agreed with the Sponsor), associating lowest level terms (LLTs) with PTs and SOC by the primary hierarchy. TEAEs are defined as AEs that started or worsened after the first administration of IMP and to the EOT visit or start of another SRL treatment, whichever comes first. Furthermore, the onset date of an TEAE should be prior to the date of last dose of IMP + 5 half-lives (5x10.6 days).

TEAEs, presented as SOC and PTs, will be further defined:

- Treatment period TEAEs are defined as:
  - For patients enrolled into the extension period: TEAEs that occur or worsen on or after the date of first IMP administration in the treatment period and before the date of the first IMP administration in extension period.
  - For patients early terminated from the IMP in the treatment period: all TEAEs reported are double-blind treatment period TEAEs.

The severity of all AEs will be graded using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Missing severity will be summarized as a separate category.

IMP-related TEAEs are assessed as “Probably related” and “Possibly related”. If the causal relationship to the IMP is missing, the event will conservatively be assigned as related to IMP.

TEAEs of special interest (TEAESI) will be defined pre-DBL as applicable.

An overall AE summary will be presented using the number and percent of patients, and number of events with the following:

- Any AE
- Any TEAE
- Any IMP-related TEAE, including events assessed as “Probably related” and “Possibly related”, or missing relationship to the IMP on the eCRF
- Any TEAE by CTCAE Grade
- Any IMP-related TEAE of CTCAE Grade ≥ 3
- Any TESAE
- Any IMP-related serious TEAE
- Any TEAEs leading to withdrawal from the trial
- Any TEAE leading to IMP discontinuation, including events with action taken with trial treatment = “Drug withdrawn” on the eCRF and TEAEs leading to withdrawal from the trial

- Any TEAE leading to death, including events with outcome = fatal on the eCRF
- Any TEAESI
- TEAESIs of CTCAE Grade ≥ 3
- Any injection site TEAE
- Any related non-injection site TEAESIs
- Any TEAE related to COVID-19

TEAEs will be summarized by trial period, SOC, and PT, with the number and percentage of patients and the number of events, where applicable.

The tables will display the number and percentages of patients who reported at least one AE in each SOC. Within each SOC, the tables will display the number and percentages of patients reporting at least one AE as designated by the PT. The outputs will be presented by descending frequency across all patients for a given SOC and PT. At each level of summarization, a patient will be counted once if he/she reported one or more events. The severity grade to the IMP will be summarized in a similar manner. For example, if a patient reports multiple AEs, the patient will be represented in the most severe category.

All AEs will be listed. TEAEs and non-TEAEs will be listed separately.

5.10.2 Laboratory Evaluations

The following summaries will be generated separately for hematology, biochemistry, coagulation, thyroid, HbA1c and urinalysis tests by treatment group. All laboratory values will be presented in standard international units.

- Summary table of observed values and change from baseline at each assessed visit during the treatment period.

For summary statistics, numerical laboratory measurements values below the lower limit of detection or above the upper detection limit will be replaced by the detection limit reported by the laboratory. In the listings, values will be reported as originally recorded, and in SI units.

In addition to the summary tables above, box plots of observed laboratory test results will be presented.

Laboratory tests for which NCI CTCAE toxicity grading is available will be tabulated separately. For laboratory tests where grades are not defined by CTCAE, results will be categorized by abnormality grades (e.g. low clinically significant/low not clinically significant/normal/high not clinically significant/high clinically significant/missing) based on reference normal ranges. Both the CTCAE grades and abnormality grades will be provided by the central lab.

For laboratory tests where grades are defined by CTCAE, the following tables will be used. Note, lab tests with bi-directional toxicity grades (e.g. hemoglobin decreased [anemia] vs hemoglobin increased) available will be summarized separately under each direction.

- Summary of worst post-baseline CTCAE grade (regardless of the baseline status) during the treatment period. Each patient will be counted only once for the worst grade observed post-baseline while on treatment with IMP.
- Shift from baseline to Week 53 and to the worst post-baseline CTCAE grade during the treatment period.

For laboratory tests where grades are not defined by CTCAE:

- Shift from baseline in abnormality grades to Week 53.
- Shift from baseline in abnormality grades to worst post-baseline value during the treatment period. Where worst value is defined as the value farthest from the normal limit.

In addition, a summary of abnormal laboratory results by visit will be presented by the number and percent of patients in each treatment groups with the following:

- Alanine Transaminase (ALT) > 8x Upper limit normal (ULN)
- Aspartate Aminotransferase (AST) > 8x ULN
- ALT > 5x ULN
- AST > 5x ULN
- Alkaline Phosphatase (ALP) > 2x increase from baseline
- Hemoglobin A1c ≥ 10%
- Potassium < 3.5 mmol/L
- Magnesium < 0.7 mmol/L

All laboratory results will be presented in data listings. A separate listing with laboratory test results outside of normal range will also be present.

5.10.3 Vital Signs

Weight, and vital sign results (pulse rate, respiratory rate, body temperature, systolic blood pressure [SBP], diastolic blood pressure [DBP]), and change from baseline values will be presented in data listings by treatment group and patient. Abnormal findings will be flagged (abnormal not clinically significant/abnormal clinically significant).

Weight, and vital sign results will be summarized descriptively using observed values and changes from baseline by treatment group and each visit/at scheduled timepoint for the safety analysis set (SAF).

Box plots of weight and vital sign results will be presented by treatment group and visits for the safety analysis set (SAF).

5.10.4 Electrocardiogram (ECG)

The 12-Lead ECG will be collected in triplicate. The average value of the triplicates at each time point will be used in summaries described below.

ECG parameters (PR, QRS, QT, QTc corrected by Fridericia's formula [QTcF], and RR intervals) will be summarized descriptively using observed values and change from baseline by treatment groups and scheduled visits/timepoints.

Categorical analysis of QT/QTc interval data based on the number and percentage of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented by treatment arm at each scheduled assessment time point. Categorical analysis of QTcF data will be presented using the boundaries in Table 7.

Table 7: QTcF interval boundaries

QTcF Interval	Criteria (ms)
Observed QTcF interval	≤ 450 msec > 450 to ≤ 480 > 480 to ≤ 500 > 500
Change from baseline in QTcF interval	≤30 >30 to ≤ 60 >60

In addition, shift from baseline of investigator's overall ECG evaluation (i.e., normal, abnormal not clinically significant, abnormal clinically significant) at each post-baseline visit will be summarized using counts and percentages of patients.

All ECG results and overall ECG evaluation will be presented in data listings by treatment group and patient. Abnormal values will be flagged and categorized as 'abnormal not clinically significant' or 'abnormal clinically significant').

5.10.5 Physical Examination

Data collected on each physical examination body system eCRF page will be listed but not summarized. Abnormal findings will be flagged (abnormal not clinically significant/abnormal clinically significant).

Any abnormal, clinically significant physical examination results recorded as MH or AEs, will be summarized accordingly in the AE or MH summary tables.

5.10.6 Additional Safety Assessments

5.10.6.1 Gallbladder Examination

Gallbladder imaging results details (location of gallstones, gallbladder sludge, or other findings) will be listed for each patient at each assessed visit.

5.11 Pharmacokinetic Analyses

All individual plasma octreotide concentration data for CAM2029 will be listed. Individual concentration-time profiles will be displayed graphically by patient on the linear and semi-log view.

The PK analysis set will be used for all summaries of plasma octreotide concentrations in this section unless specified otherwise.

Descriptive statistics (n, m [number of non-zero concentrations], arithmetic mean, coefficient of variation percentage mean, standard deviation, median, geometric mean, coefficient of variation percentage geo-mean, minimum and maximum and 95% CIs of the mean) for octreotide concentration will be presented at each scheduled time point by CAM2029 dose regime. Concentration values below the limit of quantification (BLOQ) will be treated as 0 for the computation of descriptive statistics.

Summary concentration-time profiles will be displayed graphically.

[redacted]

Possible derivation and analyses of PK parameters, Population PK analyses, PK/efficacy analyses and PK/safety analyses including data from this trial is outside the scope of this statistical analysis plan and will be performed and reported separately, if applicable.

5.12 Pharmacodynamic Analyses

[redacted]

5.13 Immunogenicity Analyses

Blood samples for immunogenicity assessment of ADA will be taken according to the protocol Table 3.

ADA status (e.g. positive, negative) will be summarized by frequency counts and percentages at each assessment time point. In addition, number and percentages of patients with positive ADA responses at any post-baseline assessments will be summarized. Titer values will be summarized descriptively.

If presence of ADA, the neutralizing capacity of the antibodies (NAb) will be analyzed and presented in listings.

All immunogenicity results will be present in a data listing.

5.14 Interim Analyses, Timing of Analyses, and Data Monitoring Committee

[redacted]

5.15 Changes to Protocol-planned Analyses

[redacted]

6 SAMPLE SIZE DETERMINATION

The sample size calculation is based on a trial by Hogan et al comparing pasireotide to placebo (2). In this trial, the comparison between pasireotide and placebo over 12 months resulted in a treatment difference in reducing htTLV of approximately 235 mL/m, or 9-10% expressed as percent change from baseline. The residual SDs with the 2 analysis approaches were approximately 170 mL/m and 8%.

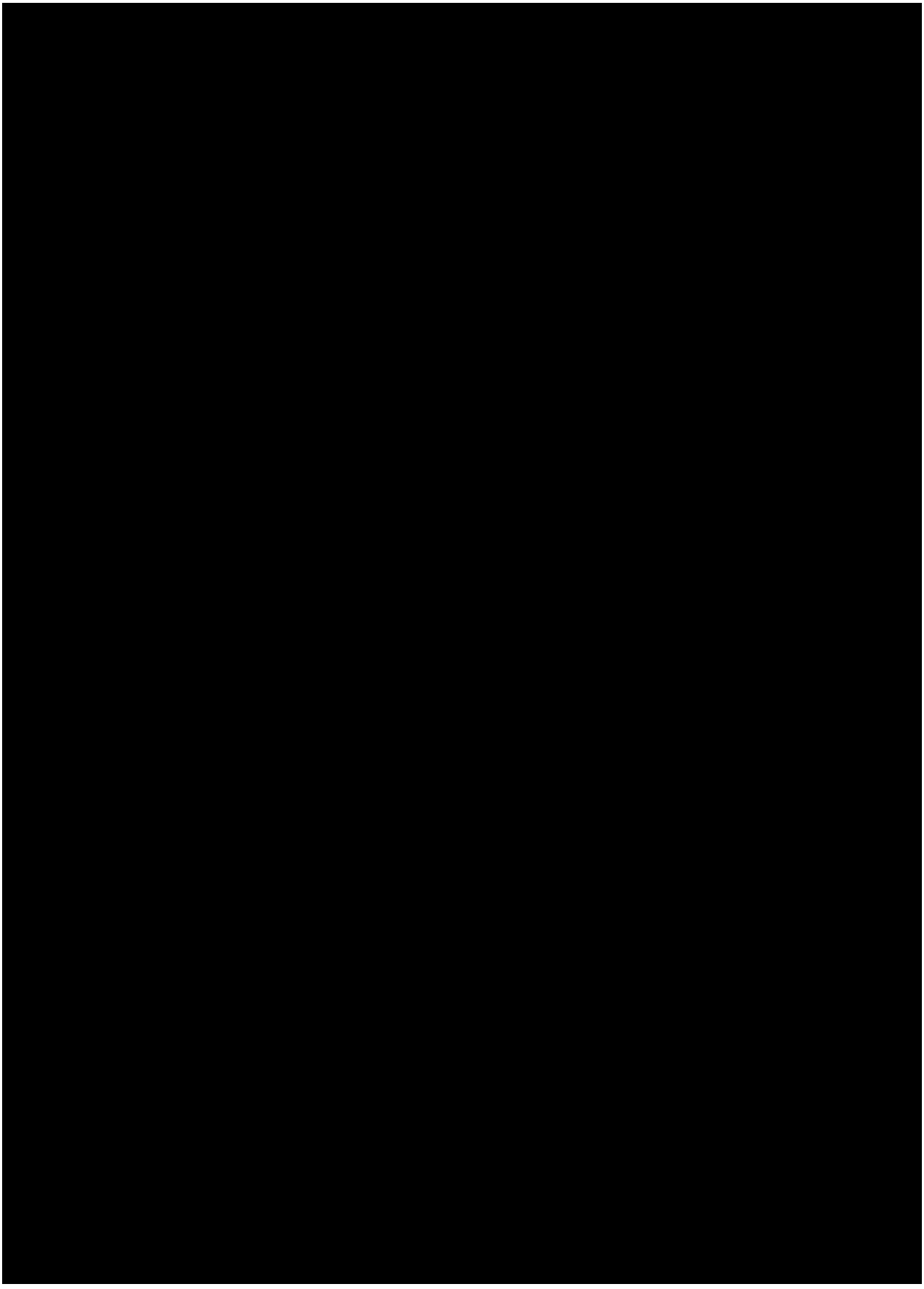
With 20 patients per treatment arm, the power is 80% if the true treatment difference is 165 mL/m (approximately 70% of the difference seen in the Hogan trial (2)). This calculation is based on an assumed residual SD of 180 mL/m using a t-test with a significance level of 5% (two-sided). With the same assumptions, the smallest observed treatment difference to give $p < 0.05$ is approximately 115 mL/m. If the two CAM2029 treatment arms are combined in the comparison to placebo, the number of patients in the comparison will be 40 vs 20. Assuming the same treatment difference, 165 mL/m, the power is approximately 90%. For a treatment difference of 141 mL/min, the power for the combined comparison would be approximately 80%.

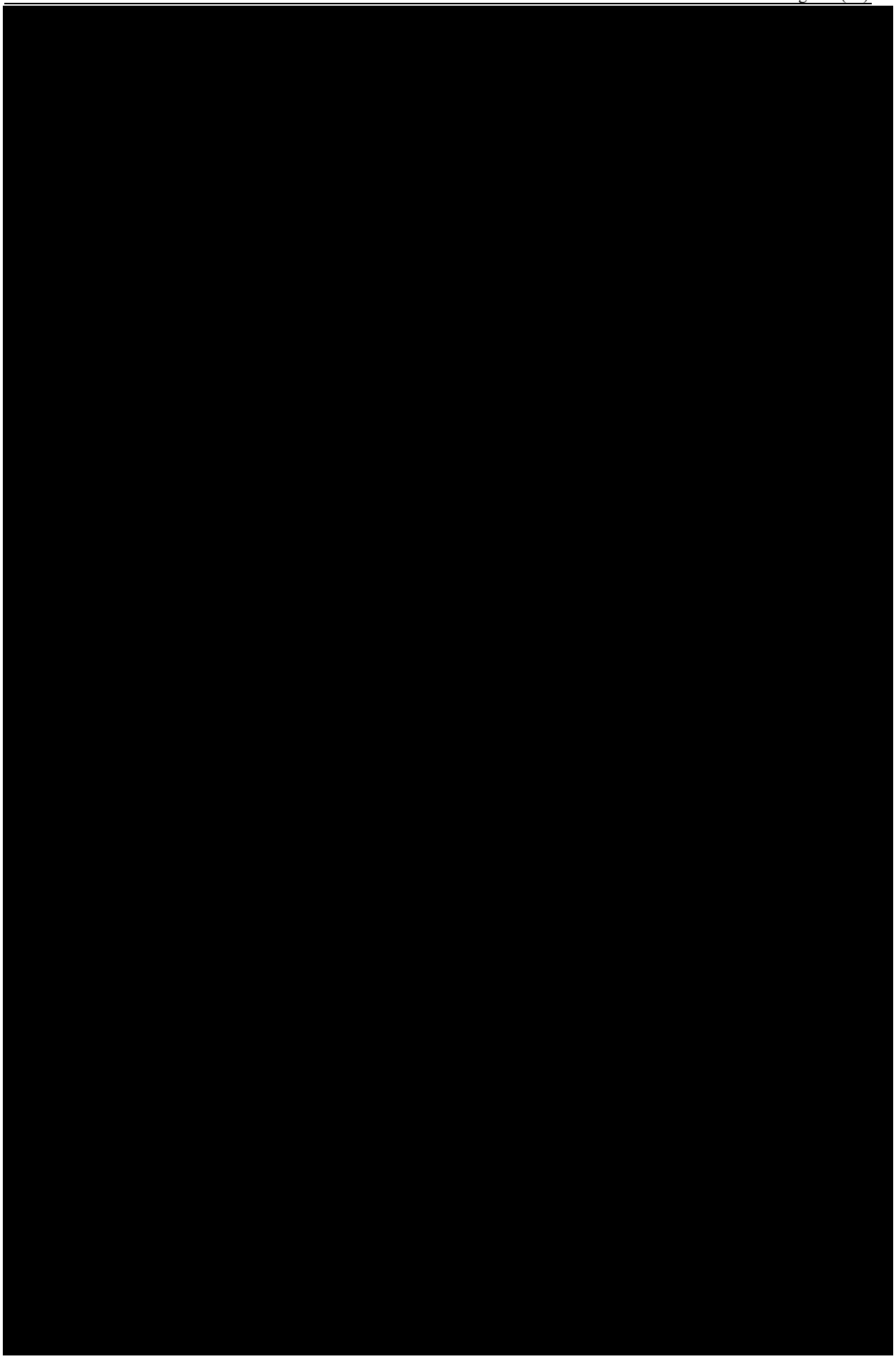
With an assumed 15% drop-out rate the total number of patients required in the trial was estimated to be 69.

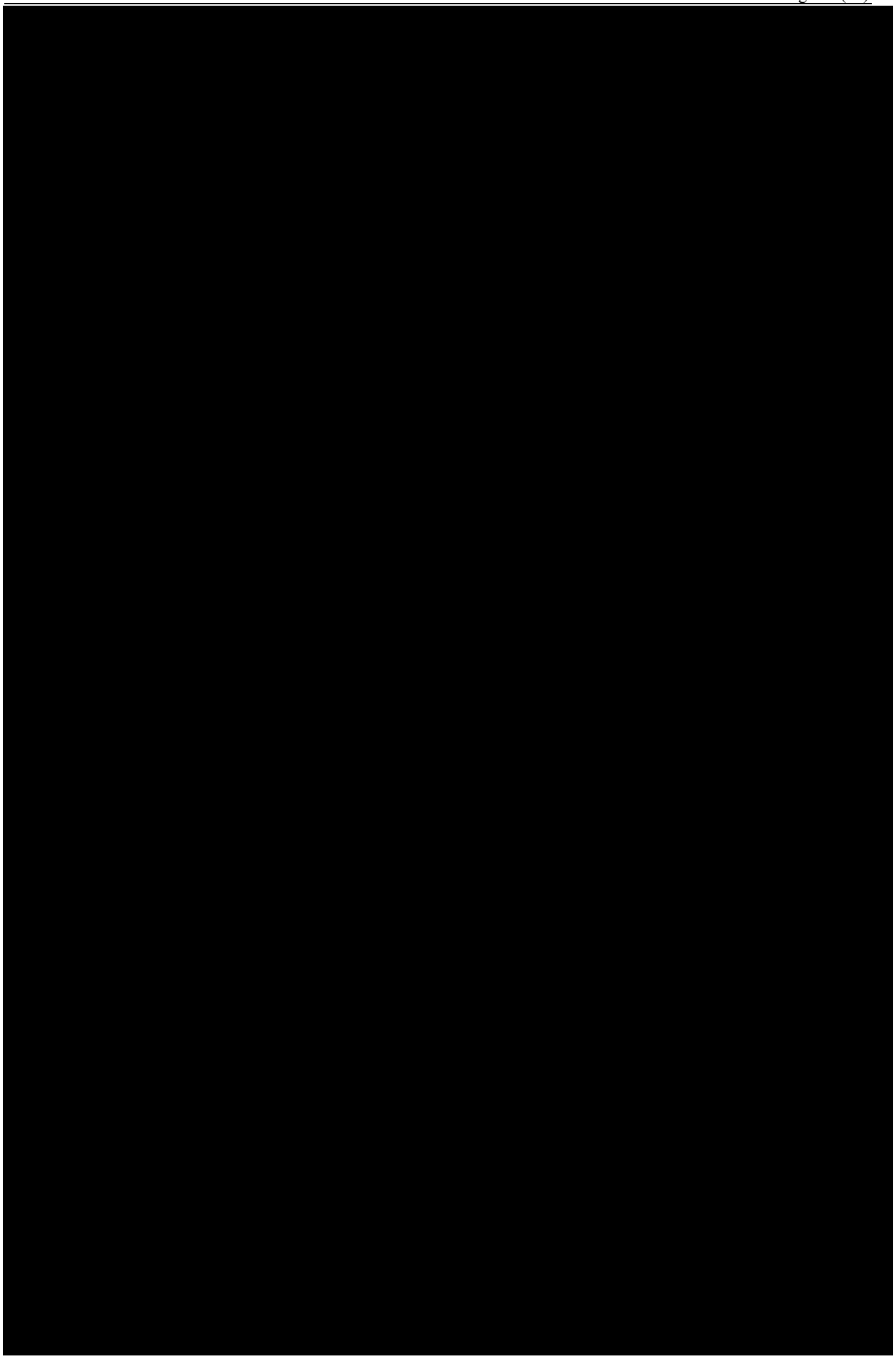
7 REFERENCES

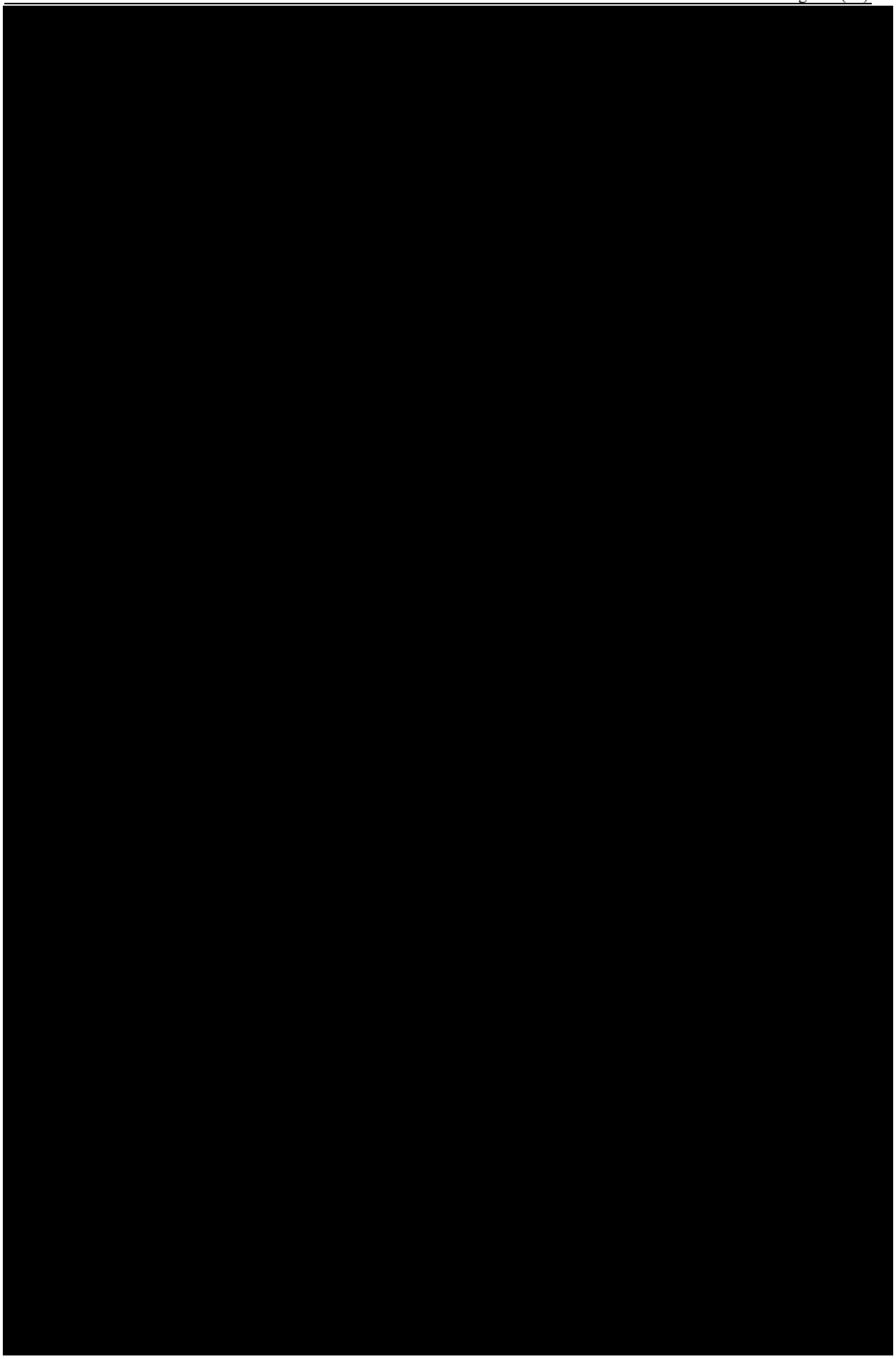
1. [redacted]
2. Hogan MC, Chamberlin JA, Vaughan LE, Waits AL, Banks C, Leistikow K, et al. Pansomatostatin Agonist Pasireotide Long-Acting Release for Patients with Autosomal Dominant Polycystic Kidney or Liver Disease with Severe Liver Involvement. CJASN. 2020;15:1267-78.
3. [redacted]
4. Ratitch B, O'Kelly M, Tosiello R. Missing Data in Clinical Trials: From Clinical Assumptions to Statistical Analysis Using Pattern Mixture Models. Pharm Stat. 2013;12:337-47.

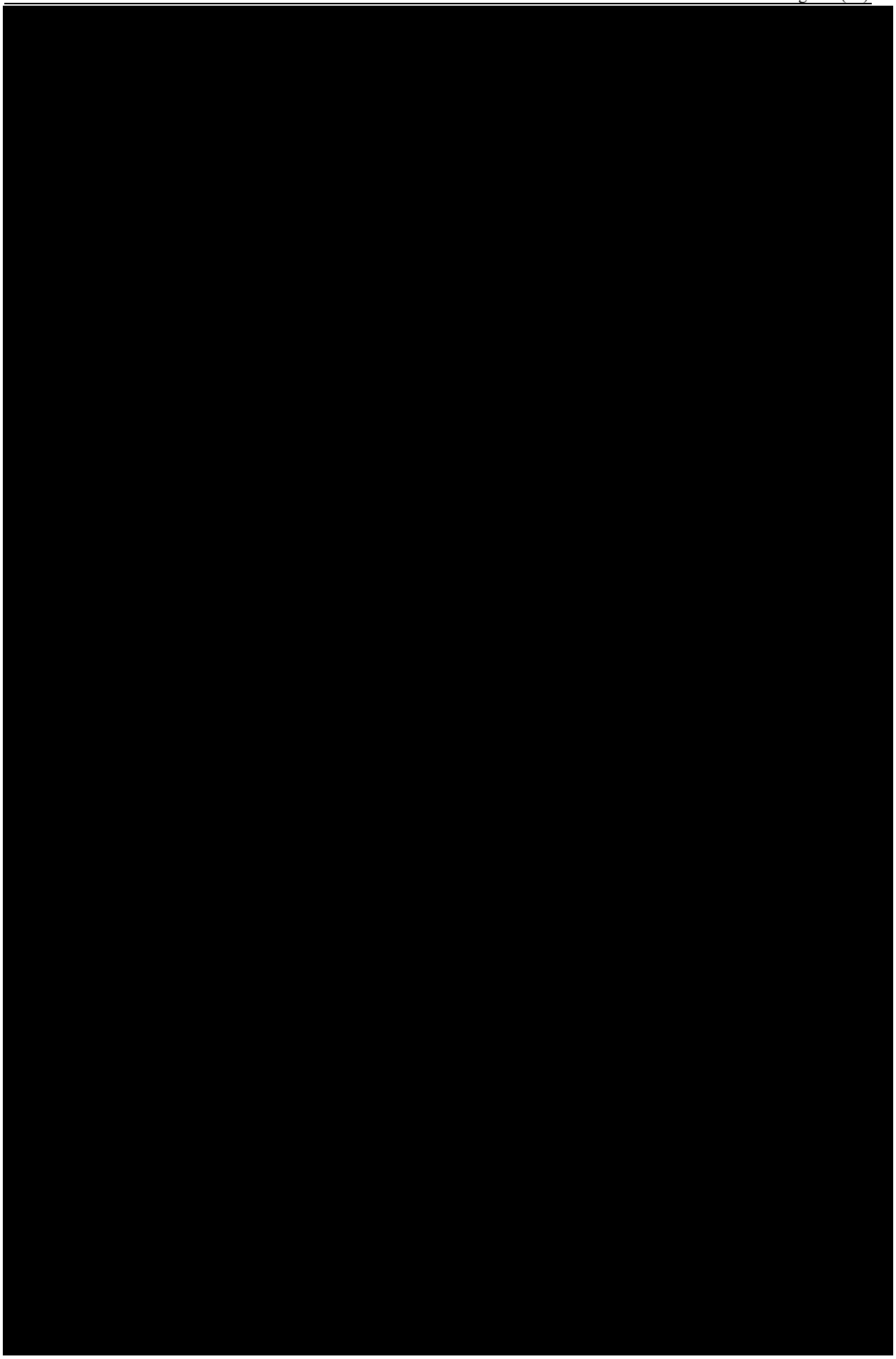
8 APPENDICES

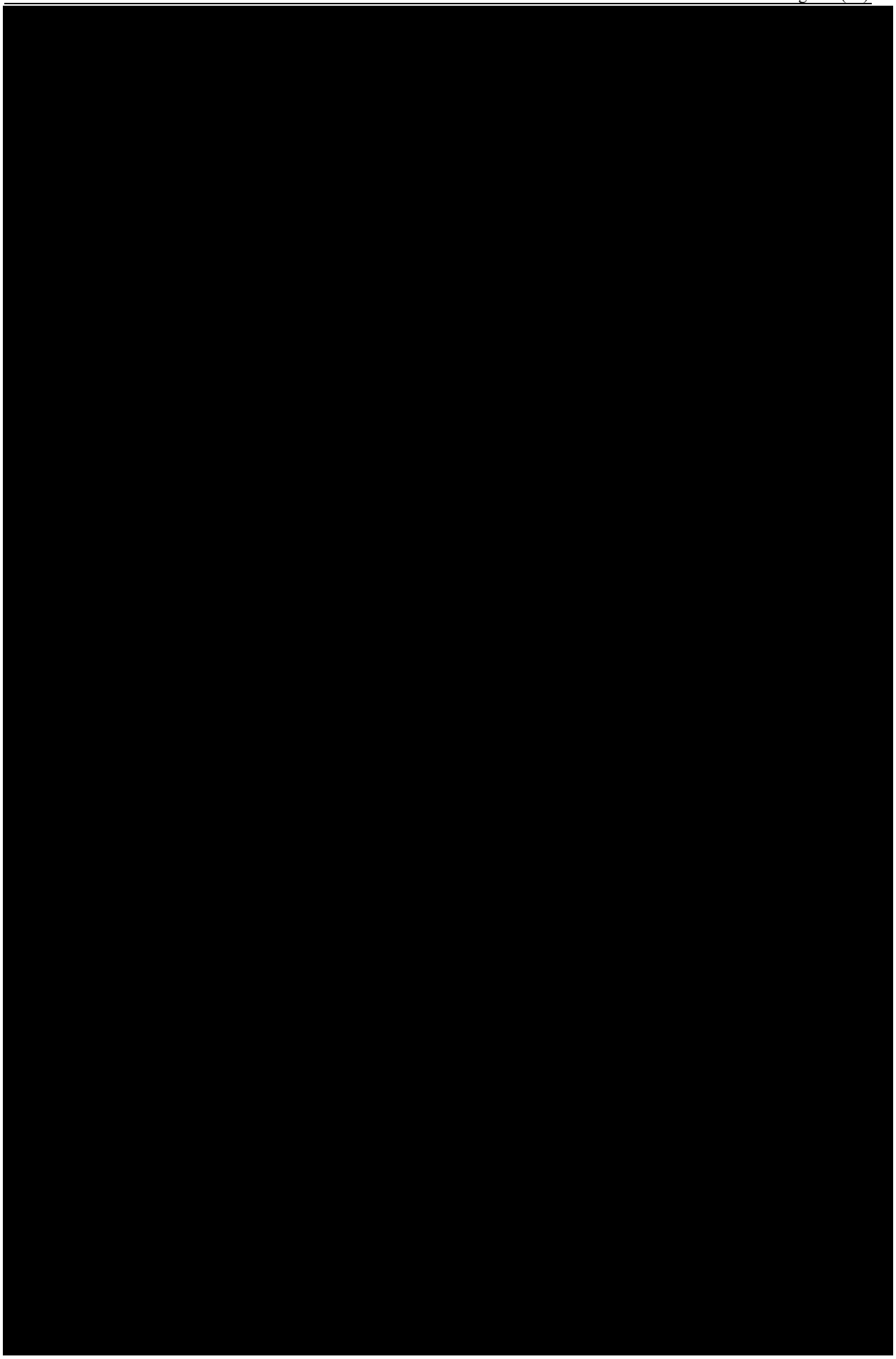


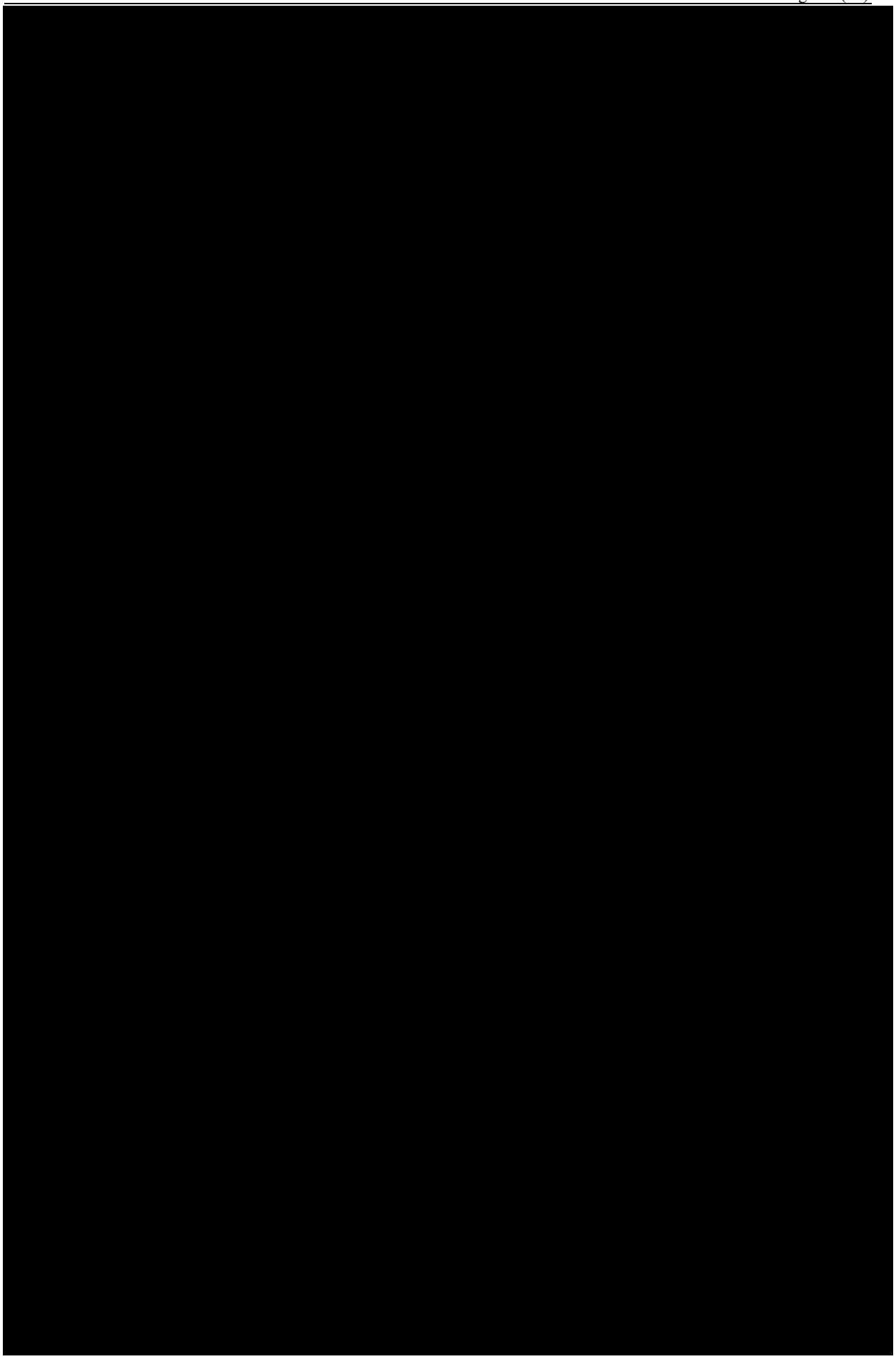


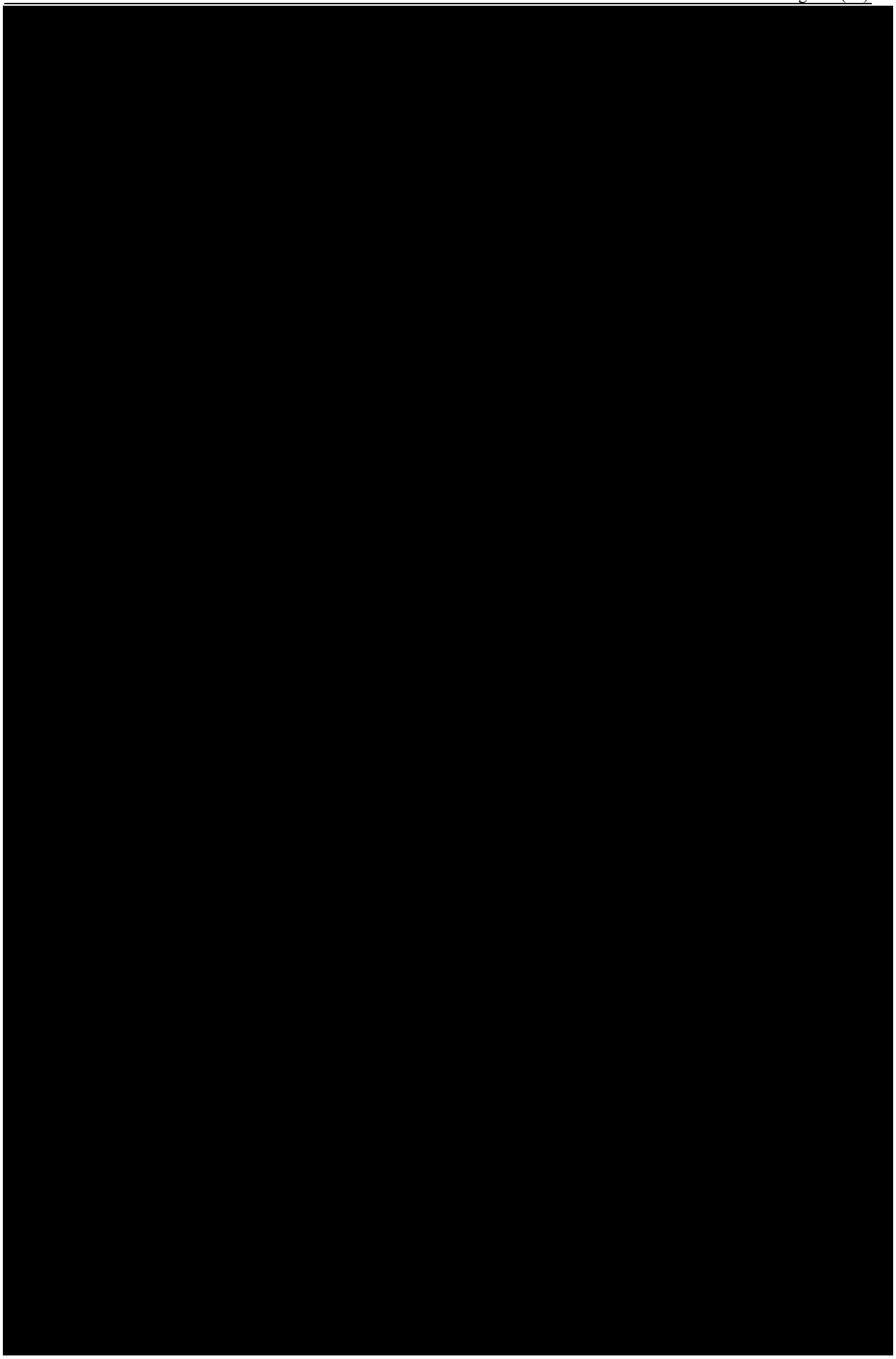


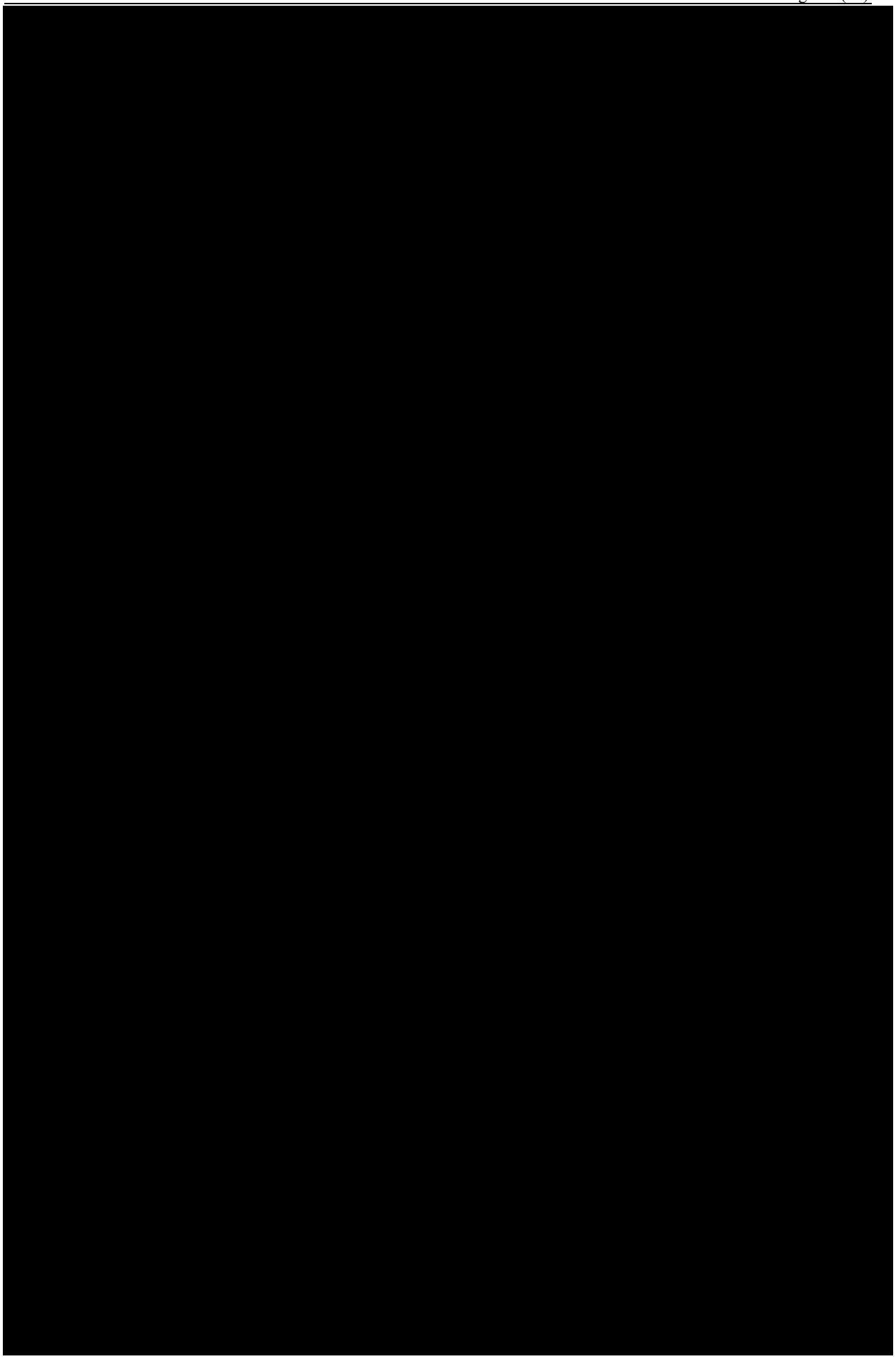


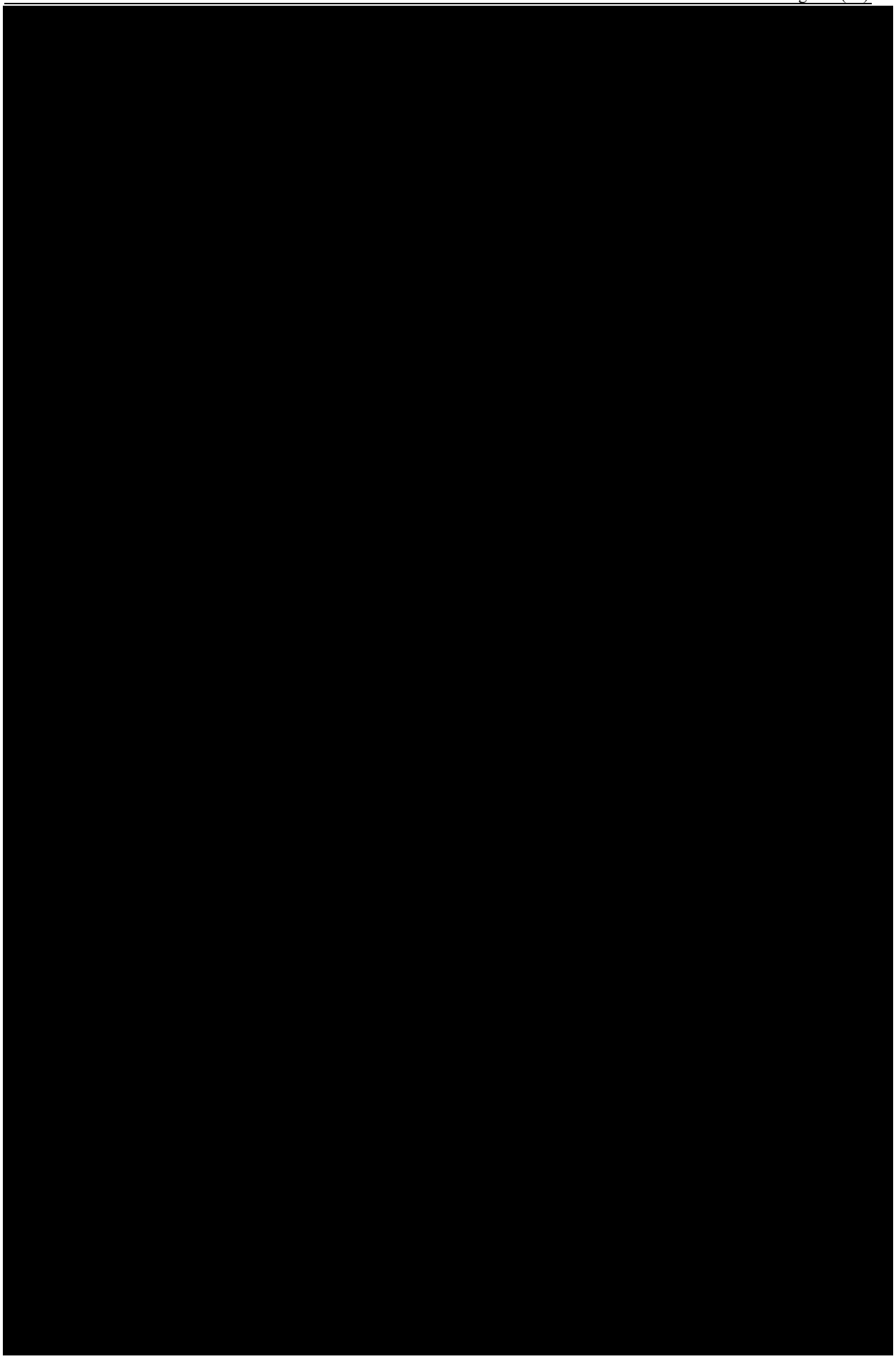












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