SANDOZ

Statistical Analysis Plan

Sandoz Global Clinical Development

Protocol Number: 21-VIN-0166

Protocol Title: A Randomized, Open Label, Multi-centre, Two-treatment, Two-period, Two-sequence, Two-stage, Multiple Dose, Steady-state, Crossover, Bioequivalence Study of Olaparib Tablets, 150 mg (Lek Pharmaceuticals d.d.) and Lynparza® (Olaparib) Tablets 150 mg (AstraZeneca Pharmaceuticals LP), in Patients With BRCA Mutated Ovarian Cancer, Recurrent Ovarian Cancer or Metastatic Breast Cancer Under Fasting Condition

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Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN (SAP)

Version 01: [redacted]

PROTOCOL No: [redacted]

A randomized, open label, multi-centre, two-treatment, two-period, two-sequence, two-stage, multiple dose, steady-state, crossover, bioequivalence study of Olaparib tablets, 150 mg [redacted] and Lynparza® (olaparib) tablets 150 mg [redacted] in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer under fasting condition.

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[redacted]

[redacted]

Protocol No. [redacted]

Statistical Analysis Plan

Statistical Analysis Plan Signature Page

We, the undersigned, declare that we have thoroughly reviewed this guideline for completeness and accuracy with the Protocol Requirements, CRF details, Database, SOPs and ICH-GCP.

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[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

%	Percent
AE	Adverse Event
ANOVA	Analysis of Variance
$AUC_{(0-\tau)SS}$	Area under the plasma concentration versus time curve for one dosing interval at steady state
BA	Bioavailability
BE	Bioequivalence
CDSCO	Central Drug Standard Control Organization
C_{maxSS}	Maximum plasma concentration during the dosing interval at steady state
CRO	Contract Research Organization
CV	Coefficient of Variation
DCGI	Drug Controller General of India
EC	Ethics Committee
Hrs	Hours
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMR	Indian Council of Medical Research
IMP	Investigational Medicinal Product
K_3EDTA	Tri Potassium Ethylene Diamine Tetra Acetic Acid
K_{el}	The elimination rate constant associated with the terminal (log-linear) portion of the curve. Estimated by linear regression of log concentration. vs. time
LAR	Legally Acceptable Representative
LOQ	Limit of Quantification
Ltd.	Limited
PK	Pharmacokinetic
PKCS	Pharmacokinetics Concentration Set
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

[redacted]

[redacted]

SD	Standard Deviation
SOP	Standard Operating Procedure
SS	Study State
USA	United States of America
USFDA	United States Food and Drug Administration
Vd	Volume of distribution
[redacted]	

[redacted]

[redacted]

1. Administrative Structure

1.1 Study Sponsor

[redacted]

1.2 Introduction and Scope

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol [redacted] Version 01 dated [redacted] The SAP provides details on the planned statistical methodology for the analysis of the study data. This SAP outlines in detail all aspects pertaining to the planned analyses and presentations for this study. The Mock shells details like Table, listing and figure shall be generated in separate document.

The statistical analyses will be made in accordance with the ICH-E9 guidelines "Statistical Principles for Clinical Trials" and guidelines from CDSCO, US FDA regulations and applicable regulatory guidelines.

1.3 Responsibility of data management

Responsibility of providing clean data for the statistical analysis lies with data management [redacted] has captured the data in software where data cleaning and query management process are described in detail in the data management plan and the related SOPs.

1.4 Responsibility of Statistical Analysis

[redacted] Statistics team will be responsible for programming statistical analysis as per approved SAP. Statistician from [redacted] will be responsible for Pharmacokinetic analysis. The Mock shells details like Table, listing and figure shall be generated as per approved Statistical Analysis Plan (SAP).

2. Study Objectives

Primary Objective:

- To assess the pharmacokinetics and establish bioequivalence of the Test Product (Olaparib tablets, 150 mg) relative to that of Reference Product (Lynparza® (olaparib) tablets 150 mg) in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer.

[redacted]

Secondary Objective:

- To monitor the adverse events of patients and to assess safety of each of the two formulations.

3. Study design

A randomized, open label, multi-centre, two-treatment, two-period, two-sequence, two-stage, multiple dose, steady-state, crossover, bioequivalence study

3.1 General Aspects

Sample Size

Considering a maximum expected intra-patient variability of 35% based on available literature estimates, a true ratio (T/R) of 0.95, 56 evaluable patients are adequate to achieve at least 81% power at 5% level of significance to meet the bioequivalence limit of 80.00% to 125.00% at Stage 1.

Sufficient number of patients will be enrolled to have [redacted] in the Stage 1 [redacted] and Stage 2 sample size (if needed) will be decided on the basis of data (observed CV) obtained after the completion of Stage 1. Maximum sample size (Stage 1 + Stage 2) is expected, but not limited to, [redacted] This is a 2-stage design according to Potvin C method[1]. Overall expected power is 86%.

Enrollment will be continued until at least [redacted] In case additional patients are recruited, those patients will continue the study until completion/withdrawal and be included in the pharmacokinetic and statistical analyses as applicable.

Note: Patients enrolled in Stage 1 will not be eligible for Stage 2.

Investigational Products

Test Product (T)	:	Olaparib tablets, 150 mg of [redacted]
Reference Product (R)	:	Lynparza® (olaparib) tablets 150 mg. Manufactured for: [redacted]

3.2 Randomization

Randomization will be carried out using SAS® (SAS Institute Inc., USA) version 9.4 or higher. Randomization will be done in blocks using PROC PLAN such that the design is balanced. The order of receiving reference and test formulations for each patient during two-periods of study will be determined according to the randomization schedule for Stage 1 and Stage 2 (as applicable).

[redacted]

[redacted]

Randomization will be generated separately for each stage.

	Period 1	Period 2
Sequence 1	Test (T)	Reference (R)
Sequence 2	Reference (R)	Test (T)

Screening and Randomization Numbering

Each patient will be assigned a unique number that will serve to identify laboratory specimens and all documents and will be used throughout the study. If a patient fails to qualify for allocation to the study i.e. is a screen failure, his/her number must not be reused for another patient.

The screening number will be a combination of the center number, the project number and the patient number. The center number will be assigned by [redacted] to the investigative site (e.g., A, B, C, D) and subsequent sites are assigned consecutive alphabet numbers. Upon signing the informed consent form, the patient will be assigned a screening number by the Investigator. At each site, the first patient consented is assigned screening number e.g., [redacted] nd subsequent patients are assigned consecutive numbers (e.g., the second patient consented is assigned screening number [redacted] the third patient is assigned screening number [redacted] Once a screening number assigned to a patient, that number will not be reused for any other patient.

If the patient is deemed eligible for enrollment into the study and will commence dosing with IMP in Period 1, then a randomization number will be assigned. The randomization number will be assigned by a combination of Site ID and Dosing sequence (e.g., A-01 where A is Site ID and 01 is number of first patient dosed, A-02 where A is site ID and 02 is number of second patient dosed). Patient will be randomized on first come first serve basis and will be given a randomization number accordingly irrespective of their screening number.

There should be a source document maintained at the site which links the screening number to the randomization assignment number (once assigned) and this information will also be reflected in screening and enrollment log of site investigator file.

3.3 Blinding

This is an open label study. However, the bio-analyst at [redacted] will be blinded to the randomization sequence of study drug administration to each of the patient. Samples that are shipped to the analytical laboratory will not contain treatment information on the sample label.

3.4 Study Endpoints

[redacted]

This study does not have efficacy endpoints. Pharmacokinetic Assessments will be carried out for assessment of Bioequivalence.

Primary Parameters: - C_{maxSS}, $AUC_{(0-\tau))SS}$
Secondary Parameters: - C_{minSS}, T_{maxSS}, C_{avSS}, swing and percentage of fluctuation.

The key safety variables of the study are as follows:

- Relevant Medical and Medication History
- HER2 Testing
- Germline or Somatic BRCA1 and BRCA2 diagnostic test
- Physical examination
- Demography
- Vital signs (Height, weight, Blood pressure, pulse rate, respiratory rate and body temperature)
- X-ray (chest)
- ECG
- Hematology, Blood chemistry & Urinalysis
- Immunological/Serology tests (HIV, HBsAg, HCV antibody, VDRL)
- Urine Screen for drugs of abuse
- Pregnancy test for Female patients
- Adverse events/ Serious Adverse Events
- Concomitant medications

4. Analysis Populations

4.1 Randomized Population

Randomized population will include all patients who are randomized. A patient will be considered to have been randomized if patient has a randomization number assigned.

4.2 Safety Population

The safety dataset will include randomized patients who receive at least one dose of IMP. Data from subjects in this dataset will be used for the assessment of safety.

4.3 PK population

Pharmacokinetic and statistical analyses for plasma concentration versus time profile of Olaparib will be performed on the data obtained from patients included in the PK dataset.

PK dataset

[redacted]

Data from the following patients will be included in the PK dataset:

- Patients who have completed both periods and have missed samples in any period that may not affect the estimation of the $C_{max,ss}$ and/or AUC parameters and have been predetermined prior to the bioanalytical analysis to not significantly impact the overall outcome of the study;
- Patients who complied with all protocol requirements, or encountered protocol deviations that do not impact the estimation of the PK parameters.

Patients withdrawn prior to sample analysis for pharmacokinetic reasons (i.e., an event that could result in an inadequately characterized pharmacokinetic profile for olaparib) will not be included in the PK and statistical analysis.

Any decision for excluding data from the final data set will be provided with a detailed explanation and will be properly recorded and dated.

PK dataset will be defined in consultation with the sponsor at different study stages for different sets of patients, prior to initiation of sample analysis for each set of patients. This dataset will be reassessed, if required (e.g., missing concentration value due to analytical reason), upon completion of the sample analysis. The PK dataset will be finally confirmed by the sponsor prior to database lock.

5. General Aspects of Statistical Analysis

5.1 Presentation of Summaries and Analyses

Descriptive statistics of primary and secondary pharmacokinetic parameters will be computed and reported for Olaparib tablets, 150 mg.

5.2 Precision of Display

Descriptive statistics such as Mean, Median and Geometric mean will be rounded up to three digits after decimal; SD with rounded up to four digits after decimal, minimum, maximum and %CV with rounded up to two digits after decimal.

5.3 Analysis Time Points

All the assessments will be performed as mentioned in the Sampling Schedule as per Protocol.

A total of 43 blood samples each of 03 mL will be collected from each patient for PK assessment during the study.

The venous blood samples will be withdrawn from each patient in each period at the following time points:

[redacted]

[redacted]

[redacted]

The post dose blood samples will be collected with an allowable deviation of ± 2 minutes. In all instances, however, the exact time of dosing and of each sample collection must be recorded. Samples collected outside the scheduled time will be considered as protocol deviations.

Note:

1. 12.00 -hour blood sample must be collected prior to next drug administration.
2. Blood sample collection (PK samples) will be collected first if other activities are coinciding.

5.4 Methods for Handling Missing Data

All concentration value below the limit of Quantification (LOQ) will be set to "zero" for all pharmacokinetic and statistical calculation. Any missing sample will be reported as "Missing" and will not be included for pharmacokinetic and statistical analysis.

Data from patients with missing concentration values (missed blood draws, lost samples, samples unable to be quantified) may be used if pharmacokinetic parameters can be estimated using the remaining data points. Otherwise, concentration data from these subjects will be excluded from the final analysis.

In case of sample collection deviations, the actual time point of sample collection will be used for the computation of pharmacokinetic parameters.

Missing plasma samples will be handled as per [redacted]

6. Patient Eligibility and Protocol compliance

6.1 Inclusion Criteria

To be eligible for the study, patients must meet all the following inclusion criteria:

1. **First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer** maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method.

[redacted]

[redacted]

OR

Maintenance Treatment of Recurrent Ovarian Cancer maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

OR

Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method.

OR

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method.

2. Non-smoking, non-pregnant, non-lactating female patient ≥18 years of age with a body mass index (BMI) in the range of 18.50 to 30.00 kg/m^2 (both inclusive).
3. Able to give written informed consent for participation in the trial and willing to adhere to protocol requirements.
4. Patients that are already receiving a stable dose of Lynparza® (olaparib) tablets (2*150 mg tablets) 300 mg twice daily for at least 10 days.

   OR

   Patients requiring Olaparib in the dose of 300 mg (2*150 mg tablets) twice daily as per the discretion of the Investigators; these patients will be stabilized on Olaparib as a part of study and those patients that tolerate Olaparib in the dose of 300mg twice daily will be randomized in the study. Patients that do not tolerate the mentioned dose or require dose modifications for any reason will be considered as screen failure. Patients who miss 2 or more consecutive doses or more than 3 non-consecutive doses in the Dose Stabilization period will be considered screen failure.
5. Patient having an estimated survival of at least 3 months.

[redacted]

[redacted]

6. Adequate organ and bone marrow function based upon the following laboratory criteria at the time of eligibility assessment prior to dosing in period 1:

Body system	**Parameters**
Bone marrow function	a) Hemoglobin ≥9.0 g/dL b) Absolute neutrophil count ≥1500/uL c) Platelet count ≥100,000/uL d) WBC count > 3000/mm^3
Renal function	Creatinine Clearance > 50 mL/min (calculated based on Cockcroft-Gault formula)

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
8. Absence of blood transfusion in the 28 days prior to randomization.
9. **Women of non child bearing potential** with documented evidence of hysterectomy / bilateral salpingectomy / bilateral oophorectomy at least 6 months prior to IMP administration) or postmenopausal for at least 12 consecutive months.

   OR

   Women of child bearing potential must have negative pregnancy test at screening visit and before randomization and must agree to use an effective method of avoiding pregnancy (including oral, transdermal or implanted contraceptives [any hormonal method in conjunction with a secondary method], intrauterine device, female condom with spermicide, diaphragm with spermicide, absolute sexual abstinence, use of condom with spermicide by sexual partner or sterile [at least 6 months prior to IMP administration] sexual partner) for at least 4 weeks prior to IMP administration, during the study and up to 6 months after the last dose of IMP. Cessation of birth control after this point should be discussed with a responsible physician.

6.2 Exclusion Criteria

Patients who meet any of the following criteria at screening will not be enrolled in the study:

1. History of known hypersensitivity to olaparib or its components which, in the opinion of the Investigator, would compromise the safety of the patient or the results of the study.
2. Patients found positive for HIV, Syphilis, Hepatitis B surface antigen or Hepatitis C antibody at screening.
3. Have ongoing clinically significant adverse event(s) due to prior treatments administered, as determined by the investigator.

[redacted]

[redacted]

4. Patients with Pneumonitis.
5. Patients with severe hepatic impairment (Child Pugh classification category C)
6. Patients who received any chemotherapy, radiotherapy, or any other anti-cancer therapy within 4 weeks from the last dose prior to first dosing in Period 01 (or a longer period depending on the defined characteristics of the agents used).
7. History or presence of any active infection or uncontrolled systemic disease (e.g. cardiovascular disease, hypertension, diabetes mellitus etc.) or any clinically significant disease, condition, disorder or abnormal laboratory finding that, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the study results or the patient's ability to participate in the study.
8. Patient had major surgery within 4 weeks prior to first dosing in Period 01, or who have not recovered from prior major surgery.
9. In the opinion of the Investigator, the patient will not be compliant with the requirements of the study procedures.
10. Blood loss (1 unit or 350 ml) within 90 days prior to first dosing in Period 01 for the current study.
11. Receipt of an investigational medicinal product or participation in another drug research study involving IMP administration within 30 days (or 5 half-lives, whichever is longer) prior to first dosing in Period 01 for the current study.

    Note: Elimination half-life of the study drug should be taken in consideration for inclusion of the patient in the study.
12. Usage of strong and moderate CYP3A4 inhibitors (e.g., cimetidine, ciprofloxacin, grapefruit juice) or strong and moderate CYP3A4 inducers (e.g., carbamazepine, phenytoin, St. John's Wort, rifampicin) within 30 days prior to first dosing in Period 01 (refer annexure IV for full list of prohibited medications).
13. History of difficulty in accessibility of veins or intolerance to direct venipuncture.
14. Pregnant or lactating females.
15. Patient positive on Breath alcohol analyzer test at the time of baseline/randomization visit.
16. Positive on urine test for drugs of abuse (including amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, and morphine) prior to receiving the first dose of investigational medicinal product in the study.
17. History or presence of alcoholism or drug abuse.
18. Patients with psychiatric illness/social situations that would limit compliance with study requirements.

[redacted]

[redacted]

19. Difficulty in swallowing tablets.
20. Problems with fasting.
21. History or presence of clinically significant lactose, galactose, or fructose intolerance.

6.3 Withdrawal Criteria

An investigator may withdraw a patient from the study for any of the following:

1. The patient may be withdrawn from the trial at the discretion of the investigator and/or the sponsor if judged to be non-compliant with protocol/trial procedures.
2. Any major/significant deviation from the protocol that in the opinion of the investigator/sponsor may impact the patient's safety and/or the scientific integrity of the trial.
3. Any major safety concern such as (but not limited to) serious, life-threatening, or intolerable AEs that, in the opinion of the investigator and/or sponsor requires withdrawal from the study.
4. Patients who experience emesis within two times of Tmax value (i.e. 3 hours) on Day 8 or Day 16. Patients who experience emesis at any other time during the study will be evaluated for their continued participation in the study based on the investigator's and sponsor's assessment.
5. Patients who experience diarrhea (defined as three or more episodes of loose stools during a 24 hour interval) at any time during the study will be evaluated by the investigator and sponsor and a decision for continued participation in the study will be made based on the potential impact of the event on the integrity of the study results and patient's safety.
6. If a patient found positive for Coronavirus infection (COVID-19) during the study.
7. If patient requires dose modification (i.e. change from 300 mg twice daily) or dose interruption during study participation.
8. Any patient who requires the use of unacceptable concomitant medicines.
9. If a patient becomes pregnant or develops hypersensitivity to Olaparib or to any of the excipients during the course of the trial.
10. Significant inter-current illness and/or surgery that in the opinion of the investigator and/or sponsor requires withdrawal from the study.
11. Disease exacerbation/progression that in the opinion of the investigator requires interruption and/or change in therapeutic modality.
12. If the patient requires any concomitant medication, which as per judgment of the investigator may significantly interfere with the pharmacokinetic property of the study IMP.
13. If it is felt in the investigator's opinion that it is not in the patient's best interest to continue.
14. If the patient on their own, wishes to withdraw consent.
15. Missing sample(s) or incidence of AEs that affect the pharmacokinetics of the analyte, thus

[redacted]

[redacted]

preventing a planned statistical comparison.

16. Patients who miss 2 or more consecutive IMP doses or more than 3 non-consecutive doses in a given period.

Any patient withdrawal during the study along with the reason thereof shall be documented in the CRF and reported to sponsor.

The planned sample size accounts for withdrawal among the randomized patients, so withdrawn patients will not be replaced.

Irrespective of the reason of withdrawal, the patient will be requested to complete all procedures/activities required for End of Study safety assessment as far as possible.

6.4 Protocol Deviations

All protocol deviations will be listed, including those on timing window for PK sample collection. This listing will be generated for all randomized patients.

7. Statistical analysis

7.1. Dataset Definitions

7.1.1. Safety Dataset

The safety dataset will include randomized patients who receive at least one dose of IMP. Data from subjects in this dataset will be used for the assessment of safety.

7.1.2. Concentration Set (CS)

All available concentration data of analyzed PK population will be reported in a separate table as CS.

7.1.3. Pharmacokinetic Concentration Set (PKCS)

PKCS will be defined prior to start of sample analysis and will be reassessed, if required (e.g., missing concentration value due to analytical reason) upon completion of sample analysis and prior to data analysis. PKCS dataset will be used to perform assessment of steady-state.

Subjects included in PKCS needs to be approved by sponsor.

7.1.4. PK Parameter Set (PKPS)

PKPS is dataset of PK parameters for subject from PKCS dataset excluding subjects that:

- do not achieve steady-state.

[redacted]

- have other per protocol reason for exclusion from BE assessment.

PKPS will be used for Pharmacokinetic analysis and BE assessment.

8. General Aspects of Pharmacokinetic and Statistical Analysis

Pharmacokinetic for plasma concentration versus time profile of Olaparib will be performed on the data obtained from patients included in the PKPS dataset.

8.1 Pharmacokinetics analysis

Pharmacokinetic parameters C_{maxSS}, C_{minSS}, $AUC_{(0-\tau)SS}$, C_{avSS}, T_{maxSS}, Swing, percentage of fluctuation will be calculated using plasma concentration vs time profile (Actual time of sample collection) data of both investigational medicinal products in individual patients using Phoenix®WinNonlin® Software Version 8.2 or higher (Pharsight Corporation, USA).

Primary Parameters:	
C_{maxSS}	Maximum plasma concentration during the dosing interval at steady state
$AUC_{(0-\tau)SS}$	Area under the plasma concentration versus time curve for one dosing interval at steady state

Secondary Parameters:	
C_{minSS}	Concentration at the end of a dosing interval
C_{avSS}	Average plasma concentration over the steady state dosing interval
T_{maxSS}	Time of maximum measured plasma concentration over the steady state dosing interval
Swing	$[C_{maxSS}–C_{minSS}/ C_{minSS}]*100$
Percentage of fluctuation	$[C_{maxSS}–C_{minSS}/C_{avSS}]*100$

Pharmacokinetic parameters will be calculated by non-compartmental analysis using Phoenix®WinNonlin® software Version 8.2 or higher (Pharsight Corporation, USA). All pharmacokinetic parameters will be estimated from the Plasma concentration time profile data.

All concentration values below the Limit of Quantification (LOQ) will be set to "zero" for all pharmacokinetic and statistical calculations. Any missing sample will be reported as "Missing" and will not be included for pharmacokinetic and statistical analysis.

[redacted]

Data from patients with missing concentration values (missed blood draws, lost samples, samples unable to be quantified) may be used if pharmacokinetic parameters can be estimated using the remaining data points. Otherwise, concentration data from these subjects will be excluded from the final analysis.

In case of sample collection deviations, the actual time point of sample collection will be used for the computation of pharmacokinetic parameters.

Missing plasma samples will be handled as per [redacted]

9. Statistical Analysis

SAS® Software, Version 9.4 or higher will be used for statistical analysis of pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)SS}$.

9.1 Steady-state assessment

PKCS dataset will be used for steady-state assessment.

By considering the three day's morning pre-dose concentrations in a given period, steady state analysis will be performed for each subject in each period by using the linear regression analysis to obtain the p-values. The above analyses will be done using procedure PROC REG in SAS, version 9.4 or higher.

For achieving the steady state following procedure should be assessed:

Step 1: For each subject in each period the P-values should be statistically insignificant at 5% level of significance.

If, P-values are found statistically insignificant, those patients are considered to achieve steady state. If, P-values are found significant for particular subject then go for the second step. Go for second step for patients who have missing pre-dose sample for Day 6 or Day 14.

Step 2: Ratio of the pre-dose concentrations of last two pre-dose should be $\geq$ 80% or should be $\leq$ 120.00%.

In case ratio of last two pre-dose concentrations is found to be $\geq$ 80% or $\leq$ 120.00% patients will be considered to achieve steady state. If two pre-dose concentrations is found to be less than 80% or greater than 120%, patients will not be considered to achieve steady state and will be removed from bioequivalence evaluation.

9.2 BE assessment

PKPS dataset will be used for BE assessment.

9.2.1 Steps of a two stage design according to Potvin C

[redacted]

[redacted]

Stage 1:

Step1:

Evaluate the power at stage 1 using the variance estimate from stage 1, GMR of 0.95 and an α level of 0.05 for each of C_{maxSS} and $AUC_{(0-\tau)SS}$ parameters.

Before proceeding to Step 2, notify the sponsor (via email) regarding **stage 1 power and CV values. However, the other BE assessment results (e.g. GMR point estimates or confidence intervals) should not be calculated at Step 1 nor shared with the sponsor.** After a confirmatory email is received from the sponsor, proceed to Step 2.

Step 2:

Step 2.1: If power (calculated using the observed variability and GMR of 0.95) is greater than or equal to 80% for both of the parameters (C_{maxSS} and $AUC_{(0-\tau)SS}$), evaluate BE at stage 1 using an α level of 0.05 and stop regardless of whether BE is met or not.

OR

Step 2.2: If the power for either of the two parameters (C_{maxSS} or $AUC_{(0-\tau)SS}$) is less than 80%, evaluate BE using an α level of 0.0294.

Step 2.2.1: If the BE criterion is met, stop.

OR

Step 2.2.2: If the BE criterion is not met, calculate the sample size for stage 2 based on the variance estimated at stage 1, GMR of 0.95 and an α level of 0.0294, round up to nearest even number, add 20% subjects for dropouts and continue to stage 2. If the calculated sample size for stage 2 is less than 12, include at least 12 subjects in stage 2. If the GMR point estimate for any parameter (C_{maxSS} or $AUC_{(0-\tau)SS}$) is outside 80.00%-125.00% then study will not proceed for stage 2.

Stage 2

Evaluate BE at stage 2 using data pooled from both stages and an α level of 0.0294. Stop here whether BE is met or not and regardless of the power achieved.

9.2.2 Analysis of Variance

For Stage 1:

The ln-transformed pharmacokinetic parameters (C_{maxSS} and $AUC_{(0-\tau)SS}$) will be analyzed using an ANOVA model with Center, Treatment, Period (Center), Sequence, Sequence*Center as fixed effects and Patient (Within Sequence*Center) as a random effect.

Sequence and Center main effects and Sequence*Center interaction effect will be tested using Patient (within Sequence*Center) mean square from the ANOVA model as the error term. All other main

[redacted]

[redacted]

effects will be tested against residual error (mean square error) from the ANOVA model as the error term.

Main effects will be tested at the 0.05 level of significance, whereas the interaction effect will be tested at the 0.10 level of significance.

Results from each analysis of variance will include formulation least-squares means, the difference between the adjusted formulation means, the standard error associated with the difference and the associated confidence interval. The above analyses will be done using procedure PROC MIXED in SAS, version 9.4 or higher. Kenwart-Roger method for the denominator degrees of freedom will be applied.

For combined Stage 1 and Stage 2 data:

The selection of final statistical model after stage 2 will be based on the centers selected for stage 2:

- If all stage 1 centers will be used in stage 2, then the ln-transformed pharmacokinetic parameters (C_{maxSS} and $AUC_{(0-\tau)SS}$) will be analyzed using an ANOVA model with the effects of Center, Stage, Treatment, Period (Center*Stage), Sequence, Sequence*Center, Center*Stage, Sequence*Center*Stage as fixed, and Patient (Within Sequence*Center*Stage) as a random effect.

- Alternatively, if all stage 1 centers will not be used in stage 2, then the ln-transformed pharmacokinetic parameters (C_{maxSS} and $AUC_{(0-\tau)SS}$) will be analyzed using an ANOVA model with the effects of Center, Stage, Treatment, Period (Center), Sequence, Sequence*Center as fixed, and Patient (Within Sequence*Center*Stage) as a random effect.

The Sequence, Stage, Center and all included interaction effects will be tested using the Patient (within Sequence*Center*Stage) effect as the error term. All other main effects will be tested against the residual error (mean square error) from the ANOVA model, as the error term.

Main effects will be tested at the 0.05 level of significance, whereas the interaction effects will be tested at the 0.10 level of significance.

If Center*Stage effect is included in the model and is found to be significant, visual exploration of data will be performed to explain the potential reasons for this interaction.

Results from each analysis of variance will include formulation least-squares means, the difference between the adjusted formulation means, the standard error associated with the difference and the associated confidence interval. The above analyses will be done using procedure PROC MIXED in SAS, version 9.4 or higher. Kenwart-Roger method for the denominator degrees of freedom will be applied.

[redacted]

[redacted]

Note: Prior to Stage 1 ANOVA analyses and the assessment of center effect, combining of the small centers will be performed so as to assure that in each of the new, combined centers there will be a minimum of five evaluable patients and that each combined center includes at least one evaluable subject from each of the two sequences.

The small centers will be combined using the following three step procedure:

1. Centers will be first arranged in ascending order based on the number of evaluable patients per center (i.e., from smallest to largest center) and then in ascending order of site label (e.g. A to Z).

2. Starting with the smallest center, a center with less than five evaluable patients will be combined with a subsequent center. If there will be more than one center with less than five patients all these centers will be combined until at least five evaluable subjects will be available in the new, combined center. The procedure will continue with the next center in the arranged order, until all combined centers include at least five evaluable subjects.

3. Starting with the first combined center, a combined center with all subjects from either TR or RT sequence will be joined with the subsequent center until all combined centers include at least one evaluable subject from each of the two sequences.

The combined centers (instead of the original centers) will be used in both stage 1 and stage 2 analyses.

Note: Analysis of study will be performed as per latest/updated Statistical Analysis Plan (SAP).

9.2.3 Intra-Subject Variability

Intra-subject variability will be calculated using mean square error of ANOVA for ln-transformed analysis of C_{maxSS} and $AUC_{(0-\tau)SS}$ for Olaparib.

9.2.4 Power

Power will be calculated as per section 9.2.1 and will be reported for C_{maxSS} and $AUC_{(0-\tau)SS}$.

9.2.5 Two one-sided tests for bioequivalence

90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence intervals for the difference between least squares means of test and reference formulations will be calculated using mean square error, obtained in ANOVA, for ln-transformed C_{maxSS} and $AUC_{(0-\tau)SS}$. 90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval for the geometric least squares means ratio will be obtained by taking the exponent of lower and upper limits of 90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval, obtained for the least squares means difference.

Two one-sided test, namely Schuirmann's test, will be employed at 5% level of significance for the

[redacted]

[redacted]

lower and upper limits of 90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval to check whether the 90% (if power is more than 80% at stage 1) & 94.12 (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval for C_{maxSS} and $AUC_{(0-\tau)SS}$ will be entirely within the bioequivalence limits of 80.00% to 125.00%.

9.2.6 Ratio Analysis

Geometric least squares means for test and reference formulations will be obtained by taking the exponent of least squares means of test and reference formulations for ln-transformed C_{maxSS} and $AUC_{(0-\tau)SS}$. Ratio will be obtained by taking the exponent of difference of least squares means of test to reference formulations for ln-transformed C_{maxSS} and $AUC_{(0-\tau)SS}$. The comparisons of interest are T vs. R, so the ratios determined will be of the form T/R, where T = Test formulation and R = Reference formulation.

9.2.7 Bioequivalence criteria

For Stage 1 with Power $\geq$ 80%:

Based on the statistical results of 90% confidence intervals for the geometric least squares means ratio for the ln-pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)SS}$ for Olaparib the conclusions will be drawn whether test formulation is bioequivalent to reference formulation under Fasting condition. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric least squares means ratio of C_{maxSS} and $AUC_{(0-\tau)SS}$.

For Stage 1 with Power < 80% and for Stage 2, if required:

Based on the statistical results of 94.12% confidence intervals for the geometric least squares means ratio for the log-transformed pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)SS}$ for Olaparib the conclusions will be drawn whether test formulation is bioequivalent to reference formulation under Fasting condition. Acceptance range for bioequivalence is 80.00%-125.00% for 94.12% confidence intervals of the geometric least square means ratio of C_{maxSS} and $AUC_{(0-\tau)SS}$.

9.2.8 Clinical Data – CDISC Study Data Tabulation Model

Domains will be mapped to CDISC (Clinical Data Interchange Standards Consortium) SDTM, SDTM IG (Implementation Guide). All versions valid as per FDA Data Standards Catalog will be used for SDTM. No derived data required for analysis will be included in the SDTM domains. The SAP will not be amended to provide information on additional SDTM domains, although this will be allowed if necessary. All SDTM domains will be fully documented with define documents (DEFINE.XML) and a clinical study data reviewer's guide after database lock and final analyses are completed. Validation of CDISC SDTM domains will be done using Pinnacle 21 Community (version 3.1.2 or higher).

[redacted]

[redacted]

9.2.9 Analysis Data – CDISC Analysis Data Model

All planned and exploratory analyses will be completed using the ADaM (Analysis Data Model) data sets (ADaM, ADaM IG) derived from the SDTM domains for this study. All versions valid as per FDA Data Standards Catalog will be used for ADaM. Analysis data sets will contain all derived study endpoints required for analysis. All analysis data sets will be fully documented with define documents (DEFINE.XML) and an analysis data reviewer's guide (ADRG) after database lock and final analyses are completed. Validation of CDISC ADaM domains will be done using Pinnacle 21 Community (version 3.1.2 or higher)

10. Outliers

For outlier identification, appropriate statistical tests could be performed. Outliers are defined as subjects having discordant values of one or more pharmacokinetic parameters when compared with other values, e.g., a subject differs notably from the rest of the subjects for the test product response versus the reference product response. Outlier test will be performed using appropriate statistical method as per [redacted] for "Detection of Outliers". Subject data will not be removed from the statistical analysis solely based on the results of statistical outlier tests. Outlier data may only be removed from the statistical analysis if there is a real-time documentation demonstrating a protocol violation during the clinical and/or analytical phase of the BE study.

11. Evaluation of Safety Parameters (Safety Population)

All randomized patients who have received a dose of IMP will be included in safety evaluation. Results obtained when evaluating safety and tolerability (adverse events, vital signs, and clinical laboratory tests) will be listed in the report. AEs occurring prior to first IMP administration will be presented in a separate listing within study report. All AEs will be classified by System Organ Class, Preferred Term (using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0 or higher), and Severity with respect to treatment received.

11.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written study-specific informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. The investigator has the responsibility for managing the safety of individual subject and identifying adverse events. The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

[redacted]

[redacted]

Any AE (non-serious and serious) occurring after the subject has provided study-specific informed consent and until the last study visit of the subject, has to be recorded on the AE pages of the Case Report Form (CRF).

Medical conditions/diseases present before providing written informed consent are only considered AEs if they worsen after enrolment.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms;
- they are considered clinically significant;
- they require therapy.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about already known adverse drug reactions for the Investigational Medicinal Product drug can be found in the Reference Safety Information (e.g. Prescribing information).

Each adverse event should be evaluated to determine the following:

A. Severity of AEs
Adverse events should be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade refers to the severity of the AE. The CTCAE version 5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

[redacted]

[redacted]

Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL (Activities of Daily Living) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

B. Relationship to IMP

Adverse event's relationship to the study treatment should be determined (suspected/not suspected). Causality assessments are critical and must be provided for each unique AE in relation to each IMP, non-investigational medicinal product (NIMP) or other concomitant medication, if applicable. Missing causality assessments will be handled as suspected to IMP by the sponsor. The causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.

C. Evaluation of AEs (duration, action taken, outcome)

The duration (start and end dates) of adverse event should be recorded. Determine whether AE constitutes a serious adverse event (see Section 12.2.2 for definition of SAE) and which seriousness criteria have been met.

Actions taken with respect to investigation medicinal product should be documented as per the below given tabulation using CDISC STDM terminology.

[redacted]

[redacted]

Adverse Event Variable Label	CDISC STDM Terms
Action Taken with the IMP	• Dose increased; • Dose not changed; • Dose rate reduced; • Dose reduced; • Drug interrupted; • Drug withdrawn; • Not applicable; • Not known

The outcome of the adverse should be documented and assigned to one of the following categories:

Adverse Event Variable Label	CDISC STDM Terms
Outcome of event	• Not recovered/not resolved; • Recovered/resolved; • Recovered/resolved with sequelae; • Recovering/resolving; • Fatal; or • Unknown.

All AEs must be treated appropriately. The treatment of the AE should be documented in the CRF. Concomitant medication, other non-IMP treatments or changes in the administration of the IMP should be specified and documented. Treatment may include one or more of the following:

- No action taken (i.e. further observation only);
- IMP dosage adjusted/temporarily interrupted;
- IMP permanently discontinued due to this AE;
- Concomitant medication given;
- Non-drug therapy given, patient hospitalized / patient's hospitalization prolonged.

Adverse events should be recorded in the CRF under the signs, symptoms or diagnosis associated with them.

All AEs including both volunteered and the ones considered clinically relevant and reportable as AE by investigator will be recorded in the CRF and in the patient's medical records, irrespective of its association with study medications. Independent /Institutional Ethics Committee (IEC) will be informed regarding AEs as necessary.

[redacted]

[redacted]

The Most Common Adverse Events Associated with Study Medication

- Patients should be carefully monitored for adverse events/toxicity. To manage adverse events such as Myelodysplastic syndrome/Acute myeloid leukemia, Haematological toxicity, Pneumonitis, or Venous Thromboembolic Events, the dose may be reduced or interrupt the treatment.
- To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily. If a further dose reduction is required, then reduce to 200 mg taken twice daily.
- Dose adjustment is to be done by the Investigator as per the approved Summary of Product Characteristics, Prescribing Information of Lynparza® and the protocol.
- Refer Summary of Product Characteristics and Prescribing Information of Lynparza® for further information on management of AEs.

NOTE: If patient requires dose modification (i.e., change from 300 mg twice daily) or dose interruption during study participation, the patient should be withdrawn from the study.

11.2 Serious Adverse Events (SAEs)

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)] which meets any one of the following criteria:

- results in death
- is life-threatening: Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the study specific informed consent
  - General care, not associated with any deterioration in condition
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- is medically significant: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but

[redacted]

[redacted]

might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICHE2D Guidelines). All malignant neoplasms will be assessed as serious under "medically significant", if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective if a clinical event has occurred.

A **(Serious) Adverse Drug Reaction ((S)ADR) is** any (S)AE for which the investigator or sponsor assess a reasonable possibility for a causal relationship to a medicinal product.

A (Serious) Unexpected Adverse Reactions is defined as a (serious) adverse drug reaction, which is not consistent with the Reference Safety Information (e.g. Summary of Product Characteristics (SmPC), Product Monograph, Investigator's Brochure). Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events. The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'.

12. Software and Programming Considerations

12.1 Software used for Analysis

SAS® Software, Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) will be used for randomization and statistical analysis. Phoenix WinNonlin® software Version 8.2 or higher (Pharsight Corporation, USA) will be used for carrying out the pharmacokinetic analysis.

12.2 Validation for Analysis Programs

Validated programs will be used for Randomization and Analysis of variance (ANOVA) application by pharmacokinetic and biostatistics department [redacted], respectively.

13 List of Annexure

13.1 Statistical report for Justification of using Two-Stage Potvin C Design, v2

[redacted]

[redacted]

[redacted]

Statistical Report

Regarding the Justification for using the FDF Modified Two-Stage Potvin Method C Design for a Two-Period, Two Sequence, Two-Stage, Multiple-Dose Crossover Study To Assess Bioequivalence Between the Test and Reference Olaparib Products

Ver. 2

[redacted]

[redacted]

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[redacted]

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[redacted]

2 SUMMARY

The "FDF" modified two-stage Potvin Method C design is described and evaluated within.

The modifications to the original Potvin Method C [1] include two futility criteria and an adjustment to the error degrees of freedom for studies performed at multiple sites. In other words, the FDF modified two-stage Potvin Method design assumes that the site/center is included in the statistical models for assessing bioequivalence.

The evaluations are performed by calculating the estimated Type I Error rate and power of the FDF modified Potvin Method C design via simulations. The simulations are performed over the relevant grid defined by stage 1 sample size (n1) ranging from [redacted] and the coefficient of variation (CV%) in a range from 20% to 40%.

The results demonstrate that, at least over the grid defined by the n1 and CV% values, the estimated Type I Error Rate and Power are relatively close to those reported for Potvin Method C in [1], with a slight decrease in both the power and the Type I error (TIE) rate for the FDF modified method. The TIE and power of the FDF modified method is decreasing (as compared to the original Potvin Method C) with increasing CV% and decreasing stage 1 sample size (n1).

No inflation of the Type I Error rate was observed over the grid of relevant n1 and CV% values.

The estimated power does not fall below the 0.80 for any combination of relevant n1 and CV% values.

The efficiency/ cost evaluation of the FDF modified two-stage Potvin Method design indicates that using a stage 1 sample size of [redacted] (determined for a single stage design under the assumption of CV% of 35%, geometric mean ratio of 0.95, power of 80%, and alpha level of 5%) the expected power for the FDF design is increased to 0.86 (from a power of 0.80 of a single stage design) while increasing the expected mean total sample size by 4%.

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3 INTRODUCTION

PURPOSE OF THE REPORT

As per email communications beginning 1 October 2021 and under the terms and conditions agreed to with [redacted] CAIR Center has agreed to supply an operating characteristics evaluation of the FDF modified two-stage Potvin Method C Design [1], using simulation. The report is to be submitted along with the protocol in Bio-IND package material for FDA review and will later be an appendix of Statistical analysis plan.

INTRODUCTION

A two-period, two sequence, two-stage, multiple-dose crossover study to assess bioequivalence of the test and reference olaparib formulation is to be performed. The study will be conducted at multiple sites (approximately 20). Primary PK endpoints are Cmax,ss and AUCtau,ss, and a bioequivalence criteria for the geometric means ratio (GMR) 90% CI being contained within a 80%-125% range will be applied to these endpoints.

This reports describes steps taken and the simulations performed to assure that the selected two-stage design (i.e., the FDF modified Potvin Method C) controls for the Type I Error (TIE) and has satisfactory power to make the planned bioequivalence study ethical.

In Section 4 on Statistical Methodology we first define the models that will be applied in assessing bioequivalence at the first and final stage of the two-stage procedure. Next, the FDF modified two-stage Potvin Method C design will be defined, and the sample size under a single stage design (and for the stage 1 of the two-stage design) will be determined.

Results in Section 5 are split into three major components so as to include the evaluation of the operating characteristics, efficiency/ cost evaluation and the results regarding validation of the function for the FDF modified two-stage Potvin Method C design (simulations and calculations).

Appendix A provides R codes for calculating the "empiric" (estimated) power of BE studies using the FDF modified two-stage Potvin Method C via simulations (function "power.tsd.2"), and for calculating the "empiric" (estimated) power and a Type I Error (TIE) rate over a grid of relevant n1 and CV% values.

Appendix B contains tables of the estimated Type I error rate and power when the maximal total sample size is set to either 150 or 200.

[redacted]

[redacted]

4 STATISTICAL METHODOLOGY

Since 2008, a number of adaptive two-stage sequential designs for bioequivalence two-sequence, two-period, two-treatment crossover studies have been suggested and evaluated with respect to TIE rate and power (Potvin et al. [1], Montague et al. [2], Karalis et al. [3], Kieser et al. [4], Schuetz [5], Maurer et al. [6], Fuglsang [7], [8], etc.).

The Potvin Method C, introduced by Potvin et al. [1] (although criticized [4], with several adaptations/ alternatives having been suggested) still appears to be the method of choice.

For the current study we developed a modification to the original Potvin Method C, which is described in detail below, and the evaluation of the FDF modified method with regard to the Type I Error (TIE) rate and power is presented in the Results Section below.

The validity of simulation results regarding estimates of the TIE rate and Power depends primarily on the match between the actual/ planned BE evaluation procedure and the procedure for the simulation and evaluation of studies used in estimating TIE and Power.

In the case of a two-stage design, this means that every step in the actual evaluation procedure must be adequately reflected in the program for simulating studies and estimating the TIE rate and power.

For the planned BE study it was decided to apply a two-stage Potvin Method C, but with the following three modifications (see Figure 1 below):

1. To include the futility criterion of Point Estimate (PE) at stage 1 (i.e., to stop the study if PE falls outside the range of 0.80-1.25),
2. To include the futility criterion of the maximal total sample size, i.e., to stop the study if the total required sample size is greater than the pre-specified maximum (e.g., either 120, 150 or 200), and
3. To adjust/decrease the error degrees of freedom (df) for the number of sites in the BE evaluation at the first and final stage of the two stage procedure (i.e., in the estimation of the Type I Error (TIE) rate and power, using simulation).

A Potvin method C design that includes the above three modifications will in this report be referred to as the "FDF modified Potvin Method C design".

[redacted]

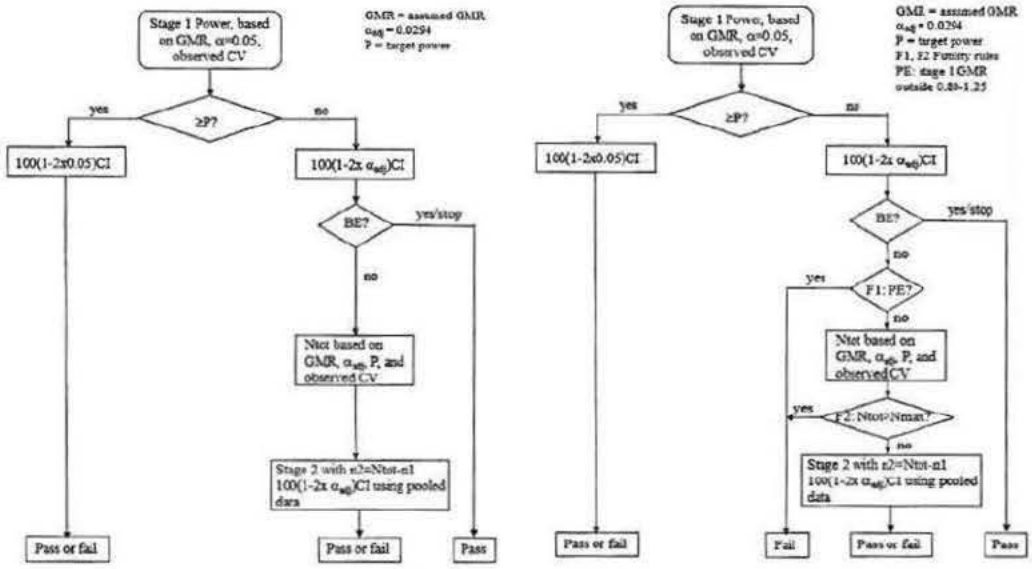

Figure 1. Potvin Method C (left) and FDF modified Potvin Method C (right) Design Schema

With the open-source R package "Power2stage", version 0.5-3. [12], several functions are provided for calculating, via simulations, the "empiric" (estimated) power of BE studies using many two-stage designs, including the Potvin Method C design. However, the modification of the Potvin Method C design by using futility criterion of PE (point 1 above) is available with the function "power.tsd.fC", whereas the modification using futility criterion of maximal total sample size (point 2 above) is available with the function "power.tsd". In other words, there is not a single function that allows for both of the futility criteria to be applied simultaneously (i.e., in the same design).

With regard to modification 3 above, no function in Power2stage allows for the adjustment of the degrees of freedom. Modification 3 must be implemented because the statistical models applied for assessing bioequivalence in the planned BE study are different than those applied in studies designed according to the standard Potvin Method C design. Functions for estimating TIE and Power in the Power2stage version 0.5-3. package can only be used for simulating data for single-site 2x2 crossover two-stage studies, and not for simulating data for more complex models.

STATISTICAL MODELS FOR ASSESSING BIOEQUIVALENCE

As displayed in Table 1 below, the models for assessing bioequivalence for studies conducted at multiple sites (i.e., under the FDF modified Potvin Method C design) are more complex than those to be conducted at a single site (i.e., under the Potvin Method C design).

[redacted]

Thus, the appropriate adjustments must be made to the function for calculating, via simulations, the "empiric" (estimated) power of BE studies using the FDF modified Potvin Method C design.

Table 1. Terms in the ANOVA models for ln-transformed PK parameters (CmaxSS and AUC(0-τ)SS) applied in the first and final stage of the two-stage Potvin Method C (left) and the FDF modified Potvin Method C design (right)

Stage	Potvin Method C design	FDF modified Potvin Method C design
1	Fixed effects: Treatment, Sequence, Period, Random effect: Patient (Sequence)	Fixed effects: Treatment, Sequence, Site, Period (Site), Sequence*Site Random effect: Patient (Sequence*Site)
Final	Fixed effects: Treatment, Sequence, Stage, Period (Stage), Sequence*Stage Random effect: Patient (Sequence*Stage)	Fixed effects: Sequence, Treatment, Site, Stage, Period (Site*Stage), Sequence*Site, Stage*Site, Sequence*Site*Stage Random effect: Patient (Sequence*Site*Stage)

It should be noted that a term for Treatment*Site interaction is not included in the ANOVA models for data from the FDF modified Potvin Method C design. The justification includes the following:

- Implementation of the standardized procedures and careful monitoring across all sites will be defined in the protocol, which should minimize a chance for the heterogeneity of the treatment effect across sites.
- According to the protocol, excessive variation in the number of subjects per site will be avoided. Small sites will be combined using a predefined procedure (to assure a minimum of five subjects per center).
- Since stage 1 sample size is determined so as to detect bioequivalence with power of at least 80%, the test for site-by-treatment interaction is potentially underpowered.
- As stated in [13] "If the treatment effect is homogeneous across centers, the routine inclusion of interaction terms in the model reduces the efficiency of the test for the main effects."

FDF MODIFIED POTVIN METHOD C DESIGN

The aforementioned three modifications were applied to the R function power.tsd (from the R package "Power2stage", version 0.5-3), where the modified function was named "power.tsd.2".

The modifications were implemented in the following three steps:

[redacted]

[redacted]

1. With regard to modification 1 above, a new argument ("fCrit") was included, and the corresponding code was transferred from the function "power.tsd.fC" (from the R package "Power2stage", version 0.5-3) to the function named "power.tsd.1".
2. Futility criterion of the maximal total sample size criterion was already included in the original function power.tsd (as the "Nmax" argument), and thus was available in the "power.tsd.1" function by setting the Nmax argument to either 120, 150 or 200.
3. With regard to modification 3, three new arguments were added to the function "power.tsd.1": "gr.ave", "gr.min" and "gr.tot", specifying the average, minimum group/site/center size, and the total available number of sites, respectively. The new function is named "power.tsd.2". (Note: "size" corresponds to the number of evaluable patients per center). The current default values of gr.ave, gr.min, and gr.tot are set to 5, 5, and 20, respectively. These values were developed from an anticipated/assumed total number of (approximately 20) sites/centers being available, and under the assumption that the smaller sites (of size less than 5) will be combined (as per the procedure described in the Study Protocol, and later in the Statistical Analysis Plan).

Technical note: The expected number of sites used at each of the two stages depends on n (the number of patients being evaluated), and consequently, the error degrees of freedom adjusted for sites depends on n and on the number of sites where these n patients were evaluated. In other words, number of sites is not a constant.

For example, using a stage 1 sample size (n1) of 60, the expected number of sites would be (60/5=) 12 (hence df=60-2-(12-1)=47), whereas for a final total sample size (ntot) of 120, the expected number of sites would be equal to the total available number of sites, e.g., 20 (hence df=120-3-(20-1) = 98). The second argument to the modified function (gr.min) is used for improved/ more accurate calculation of the adjusted degrees of freedom. A relatively accurate adjustment to the error degrees of freedom would not be possible using the single additional argument (i.e., from total available number of sites).

SAMPLE SIZE DETERMINATION FOR A SINGLE-STAGE DESIGN

As demonstrated in the Study Protocol, under the assumption of a maximum expected intra-patient variability of 35%, a true ratio (T/R) of 0.95, 56 evaluable patients are adequate to achieve at least 81% power at 5% level of significance to meet the bioequivalence limit of 80.00% to 125.00%. Thus, 56 evaluable patients are planned to be included in stage 1 of the two-stage FDF modified Potvin Method C design.

Simulations presented in the Results Section below indicate that the expected final stage power is 0.86 (i.e., 86%) of the two-stage FDF modified Potvin Method C when using stage 1 sample size of 56, assuming a CV% of 35%, and limiting the maximum total sample size to 120. The same expected power is achieved with the standard Potvin method C (for the given combination of n1 and CV%, as is demonstrated in the Results Section below).

[redacted]

[redacted]

5 RESULTS

Results are split into three major components and are presented as follows:

- Evaluation of the operating characteristics of the FDF modified Potvin Method C design,
- Efficiency/ cost evaluation of the FDF modified Potvin method C design, and
- Validation of the function for the FDF modified Potvin Method C design simulation.

EVALUATION OF THE OPERATING CHARACTERISTICS OF THE FDF MODIFIED POTVIN METHOD C DESIGN

The tables and graphs below portray (in tabular and graphical form) the estimated Type I Error (TIE) rate, power and mean total sample size for the case when the maximum total sample size is set to 120. The estimated TIE rate and power for a maximum total sample size of [redacted] are provided in Appendix B.

Estimates of the TIE rate are based on 1 million simulations, whereas the estimates of power and mean total sample size are based on one-hundred thousand simulations. This means that the standard error for TIE rate and power were set to approximately 0.0002 and 0.001, respectively.

All results are presented for stage 1 sample size (n1) ranging from [redacted] and a coefficient of variation (CV%) of 20% to 40%.

It may be observed that (at least over the grid defined by the n1 and CV% values) the estimated Type I Error Rate and Power are relatively close to those reported for Potvin Method C in [1], with a slight decrease in both the power and the Type I error rate for the FDF modified method.

Moreover, by comparing the power reported in Table 3 below with that in Table I of [1], it may be seen that the power of the FDF modified method is decreasing (as compared to Potvin Method C) with increasing CV% and decreasing n1. Thus, the highest drop (of 0.023, from 0.831 to 0.808) occurs for a CV% of 40% and a stage 1 sample size of [redacted] (Note that the decrease in power was to be expected because a reduction in error degrees of freedom yields a subsequent increase in confidence interval width.) Nonetheless, the estimated power is still above 0.80 for all relevant combinations of n1 and CV%, as long as the expected true T/R ratio is set to 0.95 (please see Table 3 and Figures 2, 3 and 4).

[1] The range for n1 is slightly extended from the initially planned range of [redacted], so as to include two n1 values [redacted] for the validation using previously published results for the original Potvin C method [1].

[redacted]

[redacted]

Likewise, by comparing the Type I Error rate of the FDF modified method with that of the original Potvin method C, it can be observed that the highest decrease (of 0.0012, from 0.0469 to 0.0457) occurs for a CV% of 40% and stage 1 [redacted] as shown in Table 2 below.

No inflation of the Type I Error rate was observed over the grid of relevant n1 and CV% values.

Table 2. Estimated Type I Error (TIE) Rate of the FDF modified Potvin C Two-Stage Design (at Theta0 of 1.25)

	n1 [redacted]							
CV								
20%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
22%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
24%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
26%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
28%	0.0498	0.0499	0.0499	0.0499	0.0499	0.0498	0.0499	0.0500
30%	0.0492	0.0497	0.0497	0.0497	0.0497	0.0497	0.0499	0.0500
32%	0.0483	0.0489	0.0490	0.0492	0.0494	0.0495	0.0498	0.0499
34%	0.0473	0.0479	0.0479	0.0483	0.0487	0.0490	0.0493	0.0496
36%	0.0464	0.0472	0.0473	0.0473	0.0476	0.0480	0.0486	0.0487
38%	0.0461	0.0466	0.0466	0.0464	0.0469	0.0471	0.0475	0.0480
40%	0.0457	0.0464	0.0458	0.0458	0.0463	0.0463	0.0467	0.0464

[redacted]

[redacted]

Table 3. Estimated Power of the FDF modified Potvin C Two-Stage Design (at Theta0 of 0.95)

	n1 [redacted]							
CV								
20%	0.9939	0.9954	0.9963	0.9973	0.9979	0.9984	0.9987	0.9990
22%	0.9843	0.9871	0.9895	0.9915	0.9929	0.9943	0.9954	0.9964
24%	0.9673	0.9726	0.9771	0.9802	0.9837	0.9862	0.9883	0.9899
26%	0.9438	0.9511	0.9577	0.9632	0.9682	0.9727	0.9758	0.9793
28%	0.9157	0.9241	0.9327	0.9400	0.9462	0.9524	0.9577	0.9628
30%	0.8877	0.8958	0.9045	0.9133	0.9203	0.9273	0.9348	0.9410
32%	0.8635	0.8715	0.8781	0.8849	0.8936	0.9012	0.9096	0.9168
34%	0.8440	0.8530	0.8567	0.8623	0.8706	0.8764	0.8845	0.8916
36%	0.8355	0.8423	0.8402	0.8452	0.8518	0.8554	0.8624	0.8666
38%	0.8263	0.8315	0.8331	0.8347	0.8374	0.8418	0.8459	0.8494
40%	0.8083	0.8149	0.8203	0.8229	0.8261	0.8306	0.8309	0.8337

Table 4. Estimated Power of the FDF modified Potvin C Two-Stage Design (at Theta0 of 0.90)

	n1 [redacted]							
CV								
20%	0.8887	0.8986	0.9094	0.9192	0.9264	0.9335	0.9403	0.9469
22%	0.8320	0.8456	0.8585	0.8697	0.8803	0.8899	0.9004	0.9092
24%	0.7738	0.7894	0.8036	0.8153	0.8294	0.8400	0.8526	0.8619
26%	0.7165	0.7334	0.7485	0.7623	0.7755	0.7888	0.8009	0.8112
28%	0.6644	0.6808	0.6950	0.7100	0.7228	0.7362	0.7485	0.7624
30%	0.6217	0.6356	0.6476	0.6611	0.6741	0.6874	0.6996	0.7141
32%	0.5885	0.6007	0.6102	0.6197	0.6325	0.6441	0.6557	0.6679
34%	0.5683	0.5773	0.5846	0.5888	0.5988	0.6074	0.6169	0.6271
36%	0.5571	0.5641	0.5660	0.5685	0.5754	0.5826	0.5898	0.5955
38%	0.5495	0.5532	0.5580	0.5565	0.5611	0.5661	0.5720	0.5726
40%	0.5371	0.5428	0.5450	0.5438	0.5481	0.5531	0.5571	0.5554

[redacted]

[redacted]

Table 5. Estimated Mean Total Sample Size of the FDF modified Potvin C Two-Stage Design (at Theta0 of 0.95)

	n1 [redacted]							
CV								
20%	48.0	50.0	52.0	54.0	56.0	58.0	60.0	62.0
22%	48.0	50.0	52.0	54.0	56.0	58.0	60.0	62.0
24%	48.0	50.0	52.0	54.0	56.0	58.0	60.0	62.0
26%	48.0	50.0	52.0	54.0	56.0	58.0	60.0	62.0
28%	48.2	50.1	52.1	54.0	56.0	58.0	60.0	62.0
30%	48.7	50.5	52.3	54.2	56.1	58.1	60.0	62.0
32%	49.9	51.5	53.0	54.7	56.5	58.3	60.2	62.1
34%	52.0	53.2	54.5	55.9	57.4	59.0	60.7	62.5
36%	55.2	56.1	56.8	58.0	59.2	60.6	62.0	63.5
38%	59.0	59.6	60.2	61.0	61.8	62.9	64.0	65.2
40%	62.8	63.1	63.8	64.4	65.1	65.9	66.8	67.7

[redacted]

[redacted]

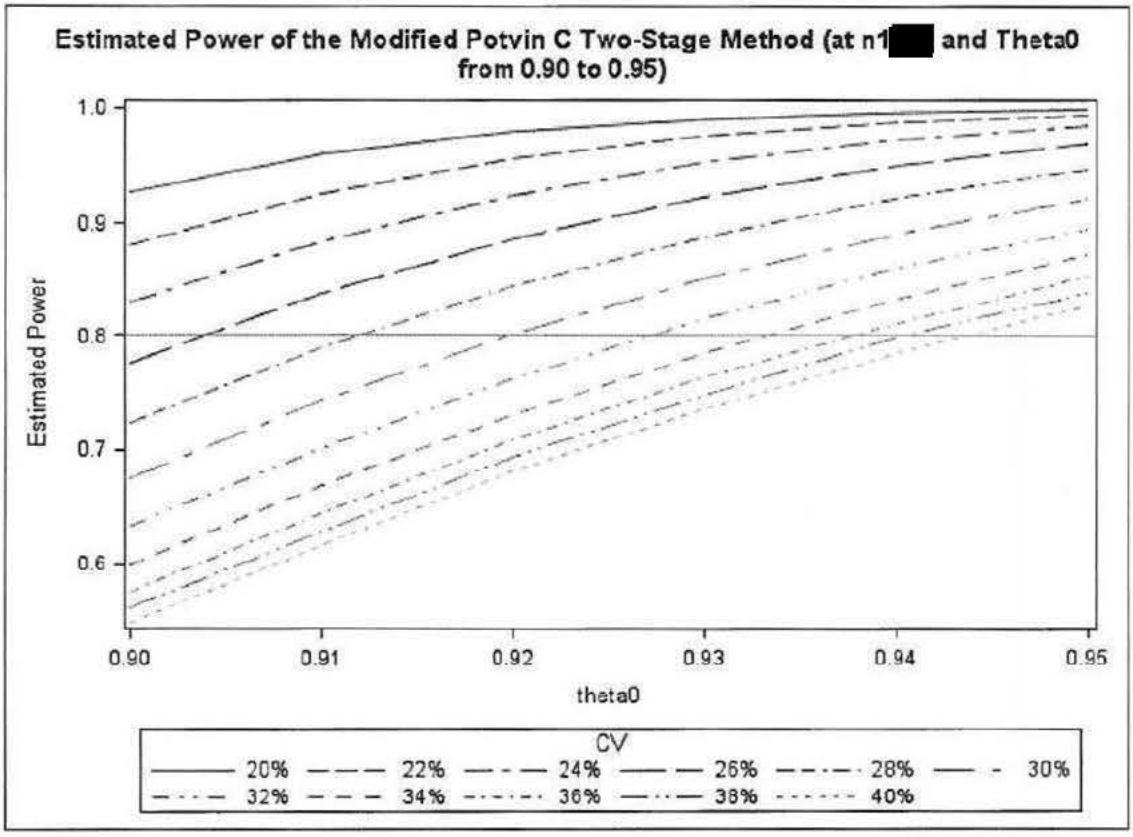

Figure 2. Estimated Power of the FDF Modified Potvin C Two-Stage Method (at n1=56 and Theta0 from 0.90 to 0.95)

[redacted]

[redacted]

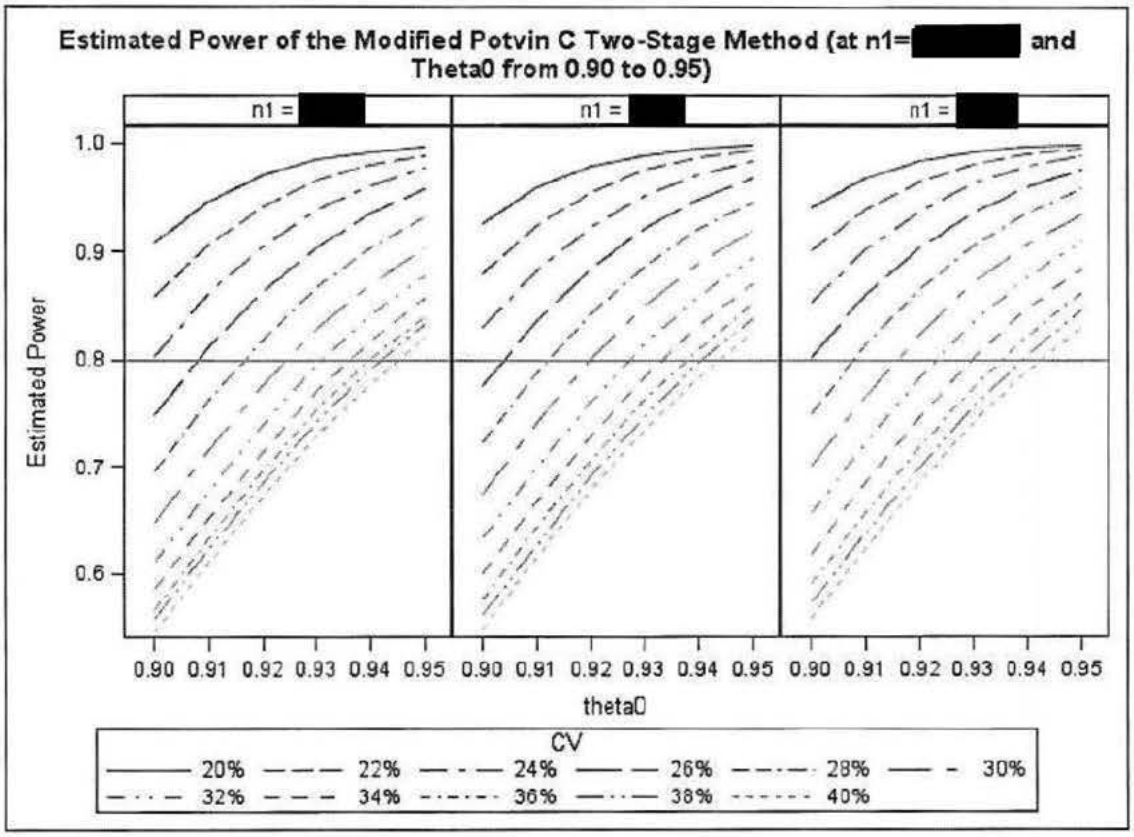

Figure 3. Estimated Power of the FDF Modified Potvin C Two-Stage Method (at n1=52, 56, 58 and Theta0 from 0.90 to 0.95)

[redacted]

[redacted]

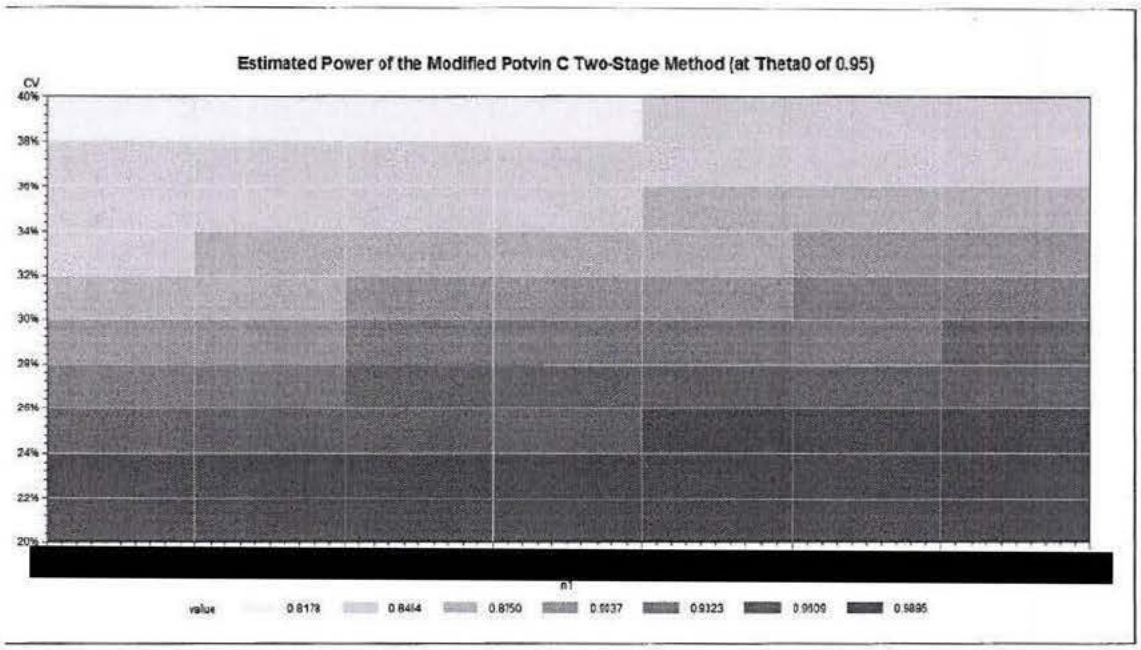

Figure 4. Estimated Power of the FDF Modified Potvin C Method (at Theta0 of 0.95)

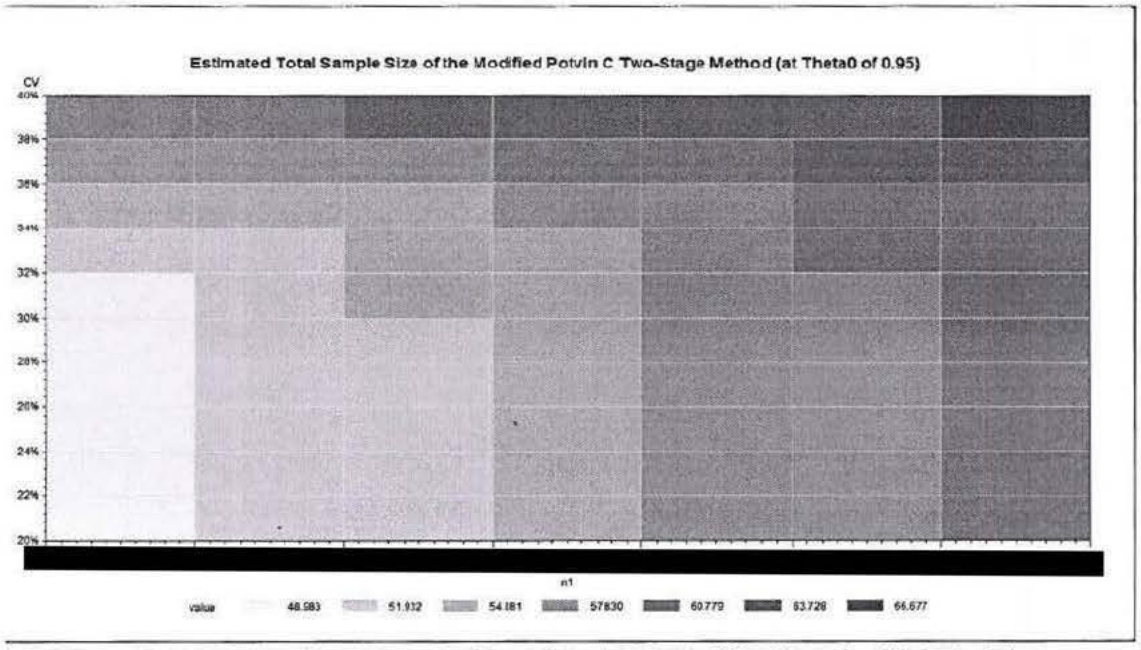

Figure 5. Estimated Total Sample Size of the FDF Modified Potvin C Method (at Theta0 of 0.95)

[redacted]

[redacted]

EFFICIENCY/ COST EVALUATION OF THE FDF MODIFIED POTVIN METHOD C DESIGN

For an assumed maximum CV% of 35%, a detailed evaluation of the expected outcomes of the FDF modified Potvin method C (based on simulated studies) is exhibited in Table 6 below for a stage 1 sample size ranging from [redacted] The expected mean total sample size is compared to the sample size of a single-stage design, i.e., [redacted] determined under the assumption of CV% of 35%, geometric mean ratio of 0.95, power of 80%, and alpha level of 5%).

It can be observed that by using a two-stage FDF modified Potvin Method C design, total/final power is increased to 86% at a cost of an expected two additional patients (i.e., an expected increase in the number of patients/cost of 4%). Only 9.8% of the studies are expected to proceed to stage 2. Of the 90.2% studies that are expected to be stopped in stage 1, 80.4% are expected to pass, whereas 9.8% are expected to fail.

By increasing stage 1 sample size to, say [redacted] the expected power is increased to 87.2%, but at the price of an expected 9.4% increase in the number of patients/cost as compared with the single-stage design.

On the other hand, if the stage 1 sample size were decreased to, say [redacted] there would be a slight decrease in expected cost/number of subject (as compared with a single-stage design), but the expected power at the final stage, and stage 1 would be decreased (from 86% to 85% and from 80.4% to 76%, respectively).

For comparison purposes, the same evaluation is performed using Potvin Method C design, as is shown in Table 7 below.

Table 6. Details of the FDF modified Potvin Method C Design Simulation Results for CV% of 35%

n1	Expected mean total N	Studies stopped in stage 1 (%)	Studies failed in stage 1 (%)	Power in stage 1 (%)	Studies in stage 2 (%)	Final power (%)	Single stage total N	Increase in # of patients/cost
[redacted]	[redacted]	78.2%	7.6%	70.5%	21.8%	83.8%	[redacted]	(4.6%)
[redacted]		81.6%	8.2%	73.4%	18.4%	84.5%		(2.8%)
[redacted]		84.9%	9.0%	75.9%	15.1%	84.8%		(0.8%)
[redacted]		87.7%	9.6%	78.1%	12.3%	85.2%		1.4%
[redacted]		90.2%	9.8%	80.4%	9.8%	86.0%		3.9%
[redacted]		92.3%	10.2%	82.1%	7.7%	86.6%		6.6%
[redacted]		94.3%	10.3%	84.0%	5.7%	87.2%		9.4%
[redacted]		95.8%	10.3%	85.5%	4.2%	87.9%		12.3%

[redacted]

[redacted]

Table 7. Details of the Potvin Method C Design Simulation Results for CV% of 35%

n1	Expected mean total N	Studies stopped in stage 1 (%)	Studies failed in stage 1 (%)	Power in stage 1 (%)	Studies in stage 2 (%)	Final power (%)	Single stage total N	Increase in # of patients/cost
[redacted]	[redacted]	78.2%	7.1%	71.2%	21.8%	84.0%	[redacted]	(5.1%)
[redacted]	[redacted]	81.9%	8.0%	73.8%	18.1%	84.4%	[redacted]	(3.3%)
[redacted]	[redacted]	85.4%	9.0%	76.3%	14.6%	84.8%	[redacted]	(1.3%)
[redacted]	[redacted]	88.5%	9.8%	78.6%	11.6%	85.3%	[redacted]	0.9%
[redacted]	[redacted]	91.0%	10.3%	80.7%	9.0%	85.8%	[redacted]	3.4%
[redacted]	[redacted]	93.3%	10.6%	82.7%	6.7%	86.4%	[redacted]	6.0%
[redacted]	[redacted]	95.2%	10.8%	84.4%	4.8%	87.1%	[redacted]	8.9%
[redacted]	[redacted]	96.6%	10.7%	86.0%	3.4%	87.8%	[redacted]	11.9%

[redacted]

[redacted]

VALIDATION OF THE FUNCTION FOR THE FDF MODIFIED POTVIN METHOD C

DESIGN SIMULATION

Comparison of TIE Rate and Power of the FDF modified Potvin C Design to those of Potvin C Design

For validation purposes, estimates of TIE rate and power (for the relevant combinations of n1 and CV%) were calculated using power.tsd function (i.e., Potvin C design) using 10^6 and 10^5 simulated studies, respectively. The results, presented in Tables 8 and 9 below were first compared to those published by Potvin et al. in Table I, and then to results for the FDF modified Potvin C design (Tables 2 and 3).

The published TIE estimates and those generated using power.tsd function agree to the third decimal place (the combinations for which the comparison was possible are shown in bold italic). Likewise, the published power estimates and those generated using power.tsd function agree to the second decimal place.

With regard to the comparison between estimated TIE rate for the FDF modified Potvin C and for the (standard) Potvin C design, the curves in Figure 6 illustrate that the difference between TIE estimates are most pronounced for small n1 [redacted] and CV% greater than, say, 35%. Estimates of the TIE rate for the FDF modified Potvin C design appear to be decreasing much faster with increasing variability (CV%) and decreasing sample size at stage 1 (n1) than that for Potvin C design.

Likewise, Figure 7 reveal that the estimated power for the FDF modified Potvin C design appear to be decreasing much faster with increasing CV% than that for the Potvin C design. This decline in power is most pronounced for stage 1 sample sizes between [redacted]

Table 8. Estimated Type I Error (TIE) Rate of the Potvin C Two-Stage Design (at Theta0 of 1.25)

	n1 [redacted]							
CV								
20%	***0.0498***	0.0498	0.0499	0.0497	0.0498	0.0499	***0.0497***	0.0500
22%	0.0498	0.0498	0.0499	0.0497	0.0498	0.0499	0.0497	0.0500
24%	0.0498	0.0498	0.0499	0.0497	0.0498	0.0499	0.0497	0.0500
26%	0.0498	0.0498	0.0499	0.0497	0.0498	0.0499	0.0497	0.0500
28%	0.0497	0.0498	0.0499	0.0497	0.0498	0.0499	0.0497	0.0500
30%	***0.0493***	0.0495	0.0497	0.0496	0.0497	0.0499	***0.0496***	0.0500
32%	0.0484	0.0488	0.0492	0.0492	0.0494	0.0497	0.0495	0.0499

[redacted]

[redacted]

	n1							
	[redacted]							
34%	0.0476	0.0478	0.0482	0.0484	0.0487	0.0493	0.0491	0.0497
36%	0.0467	0.0470	0.0475	0.0474	0.0479	0.0484	0.0484	0.0490
38%	0.0464	0.0467	0.0468	0.0467	0.0468	0.0473	0.0475	0.0479
40%	***0.0470***	0.0467	0.0464	0.0464	0.0464	0.0466	***0.0465***	0.0471

Table 9. Estimated Power of the Potvin C Two-Stage Design (at Theta0 of 0.95)

	n1							
	[redacted]							
CV								
20%	***0.9942***	0.9952	0.9967	0.9974	0.9979	0.9984	***0.9988***	0.9990
22%	0.9850	0.9873	0.9897	0.9916	0.9932	0.9948	0.9958	0.9963
24%	0.9686	0.9728	0.9772	0.9814	0.9842	0.9863	0.9887	0.9902
26%	0.9445	0.9519	0.9582	0.9642	0.9692	0.9729	0.9770	0.9797
28%	0.9160	0.9251	0.9333	0.9404	0.9475	0.9527	0.9588	0.9636
30%	***0.8865***	0.8961	0.9044	0.9134	0.9218	0.9290	***0.9357***	0.9425
32%	0.8632	0.8693	0.8773	0.8855	0.8936	0.9020	0.9092	0.9170
34%	0.8466	0.8507	0.8562	0.8621	0.8685	0.8757	0.8831	0.8907
36%	0.8382	0.8384	0.8428	0.8458	0.8499	0.8550	0.8603	0.8663
38%	0.8324	0.8348	0.8353	0.8364	0.8388	0.8410	0.8453	0.8482
40%	***0.8284***	0.8293	0.8309	0.8321	0.8333	0.8345	***0.8364***	0.8383

[redacted]

[redacted]

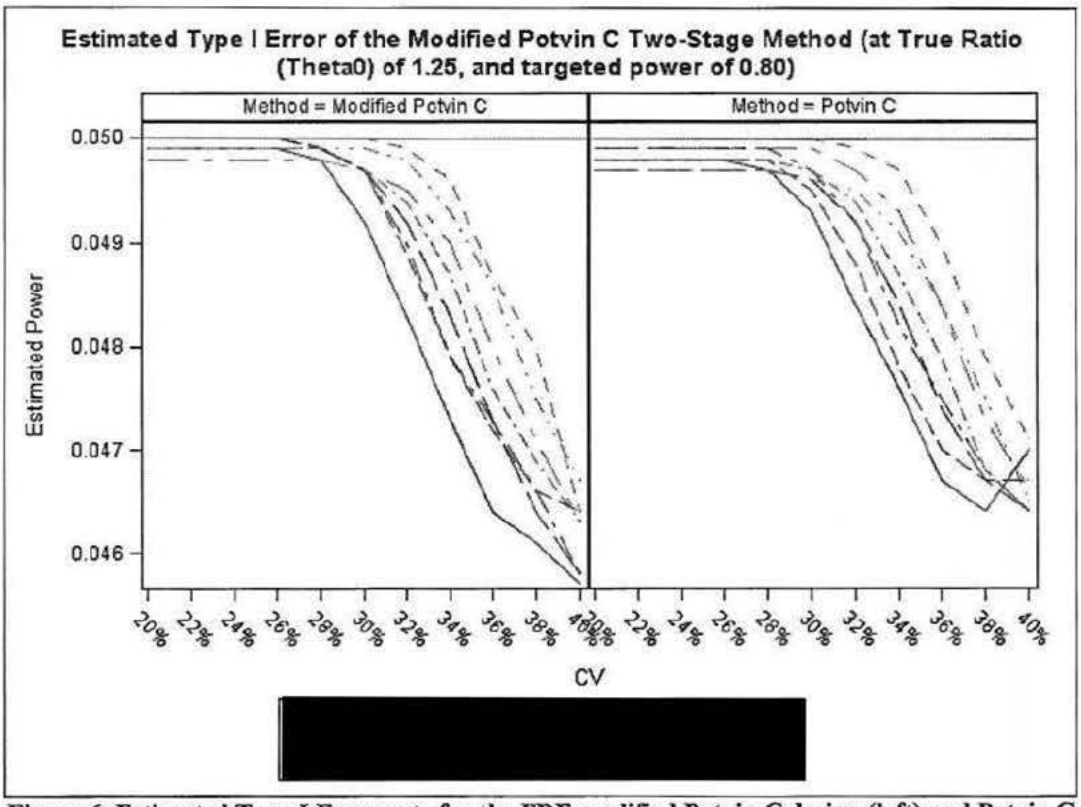

Figure 6. Estimated Type I Error rate for the FDF modified Potvin C design (left) and Potvin C design (right)

[redacted]

[redacted]

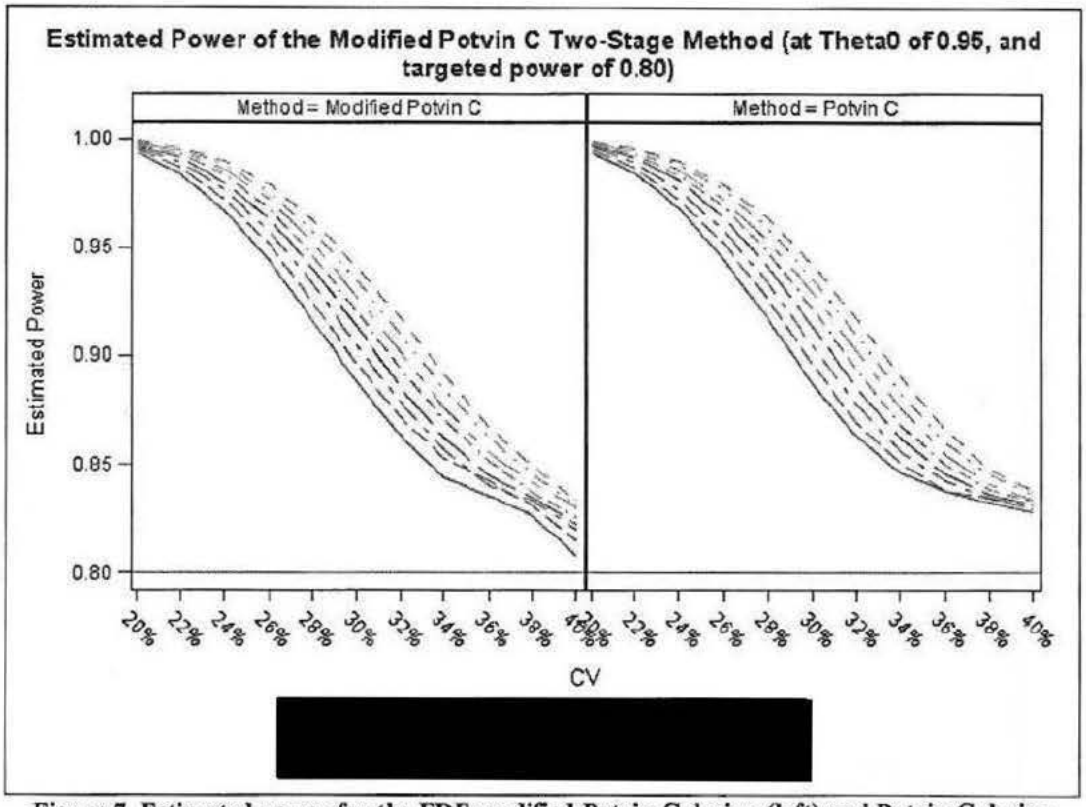

Figure 7. Estimated power for the FDF modified Potvin C design (left) and Potvin C design (right)

Step by Step Effects of Modifications to Potvin C Method

In Tables 10 and 11 are presented effects of each of the three aforementioned modification to Potvin C design regarding step by step changes in estimated TIE/ power, proportion BE in Stage 1, % Studies in Stage 2, and estimated mean total sample size (n total)

Two combinations of n1 and CV% (48, 40% and 60, 40%) were selected for step by step comparisons (i.e., from Potvin et al. [1] results to the power.tsd.2 function results), because for a lower CV% the effect of FDF modification on the power and TIE rate is almost negligible. In other words, for CV% lower than, say, 30% (and n1 in a range from [redacted], the absolute difference between the estimated power and TIE rate for the FDF modified method and those for the estimated power and TIE rate for the original Potvin C method, respectively, are less than a standard error of the simulation estimate.

Both the estimated TIE and power appear to be decreasing somewhat at each step, i.e., for each of the three FDF modifications. The same can be observed for the percentage of studies in stage 2, which decreases e.g., from 43.7% to 42.9% (by including the Futility Nmax criterion),

[redacted]

[redacted]

to 41.5% (by including the Futility PE criterion), and to 41.1% (by adjusting the degrees of freedom), as is shown in column 5 of Table 11.

The large drop in % of studies in stage 2 by including the Futility PE criterion when estimating TIE (Table 10) is to be anticipated, and can be observed/verified by applying the power.tsd.fc function from the Power2Stage package.

Table 10. Effect of FDF Modifications to the Potvin C Method on the Estimated Type I Error Rate

Potvin C Method Modifications				Estimated TIE, BE in Stage 1, % Studies in Stage 2, mean n total	
Source/ function	Futility PE	Futility Nmax	Adjustment of DF	n1=[redacted] CV%=40%	n1=[redacted] CV%=40%
Potvin C [1]	-	-	-	0.0469, na, 89.3%, 78.1	0.0470, na, 64.4%, 77..3
power.tsd	-	-	-	0.0470, 0.0317, 88.8%, 77.9	0.0465, 0.0379, 63.5%, 77.1
power.tsd	-	120	-	0.0469, 0.0317, 87.9%, 77.2	0.0465, 0.0379, 63.0%, 76.8
power.tsd.1	PE	120	-	0.0467, 0.0317, 42.7%, 62.2	0.0464, 0.0379, 30.7%, 68.3
power.tsd.2	PE	120	5, 5, 20	0.0457, 0.0323, 41.4%, 62.1	0.0467, 0.0384 30.0%, 68.4

[redacted]

[redacted]

Table 11. Effect of FDF Modifications to the Potvin C Method on Estimated Power

Potvin C Method Modifications				Estimated Power, BE in Stage 1, % Studies in Stage 2, mean n total	
Source/ function	Futility PE	Futility Nmax	Adjustment of DF	n1=[redacted] CV%=40%	n1=[redacted] CV%=40%
Potvin C [1]	-	-	-	0.831, na, 43.8, 63.9	0.836, na, 24.3%, 66.9
power.tsd	-	-	-	0.828, 0.544, 43.7%, 63.8	0.836, 0.697, 23.9%, 66.8
power.tsd	-	120	-	0.821, 0.544, 42.9%, 63.2	0.834, 0.697, 23.6%, 66.6
power.tsd.1	PE	120	-	0.818, 0.544, 41.5%, 62.6	0.834, 0.697, 23.1%, 66.5
power.tsd.2	PE	120	5, 5, 20	0.808, 0.539, 41.1%, 62.8	0.831, 0.694, 22.9%, 66.8

Reproducibility of the Results

The reproducibility of TIE rate and power results were checked using four pairs of n1 and CV% values. For power simulations, the Theta0 parameter (True geometric mean ratio) was set to 0.95, the maximal total sample size to [redacted] and the number of simulations to 10^5, whereas for TIE rate simulations, the theta0 parameter was set to 1.25, the maximal total sample size to 120, and the number of simulations to 10^6. The estimation of each of the TIE rate and power were repeated 20 times, using 20 randomly selected random number seeds.

As expected from the central limit theorem, standard deviation of TIE rate estimates is approximately equal to 0.0002, which is the estimated standard error for a proportion of 0.05 using 10^6 replications (as shown in Table 12). Likewise, the standard deviation of power estimates is approximately equal to 0.001, which is the estimated standard error for a proportion of 0.80 using 10^5 replications (as is presented in Table 13).

Table 12. Descriptive Statistics of the 20 Repeated TIE Estimates

n1	CV%	mean_TIE	stddev	min	max
[redacted]	35%	0.048289	.000234102	0.047950	0.048714
	35%	0.049058	.000240110	0.048616	0.049505
	40%	0.046328	.000184795	0.045884	0.046622
	40%	0.046657	.000229704	0.046161	0.047012

[redacted]

[redacted]

Table 13. Descriptive Statistics of the 20 Replicated Power Estimates

n1	CV%	mean_POWER	stddev	min	max
[redacted]	35%	0.85957	.000774762	0.85807	0.86063
	35%	0.87180	.001132665	0.86967	0.87389
	40%	0.82530	.001503721	0.82233	0.82797
	40%	0.83162	.001441604	0.82951	0.83416

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[redacted]

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REVISION HISTORY

Version#	Description	Date
1 (Draft)	Original/initial document	08 Nov 2021
1 (Final)	Final Document with Hyperlinks	11 Nov 2021
2	Table 1 adjusted, a paragraph added below Table 1, Reference 13 added First page adjusted	10 Nov 2022

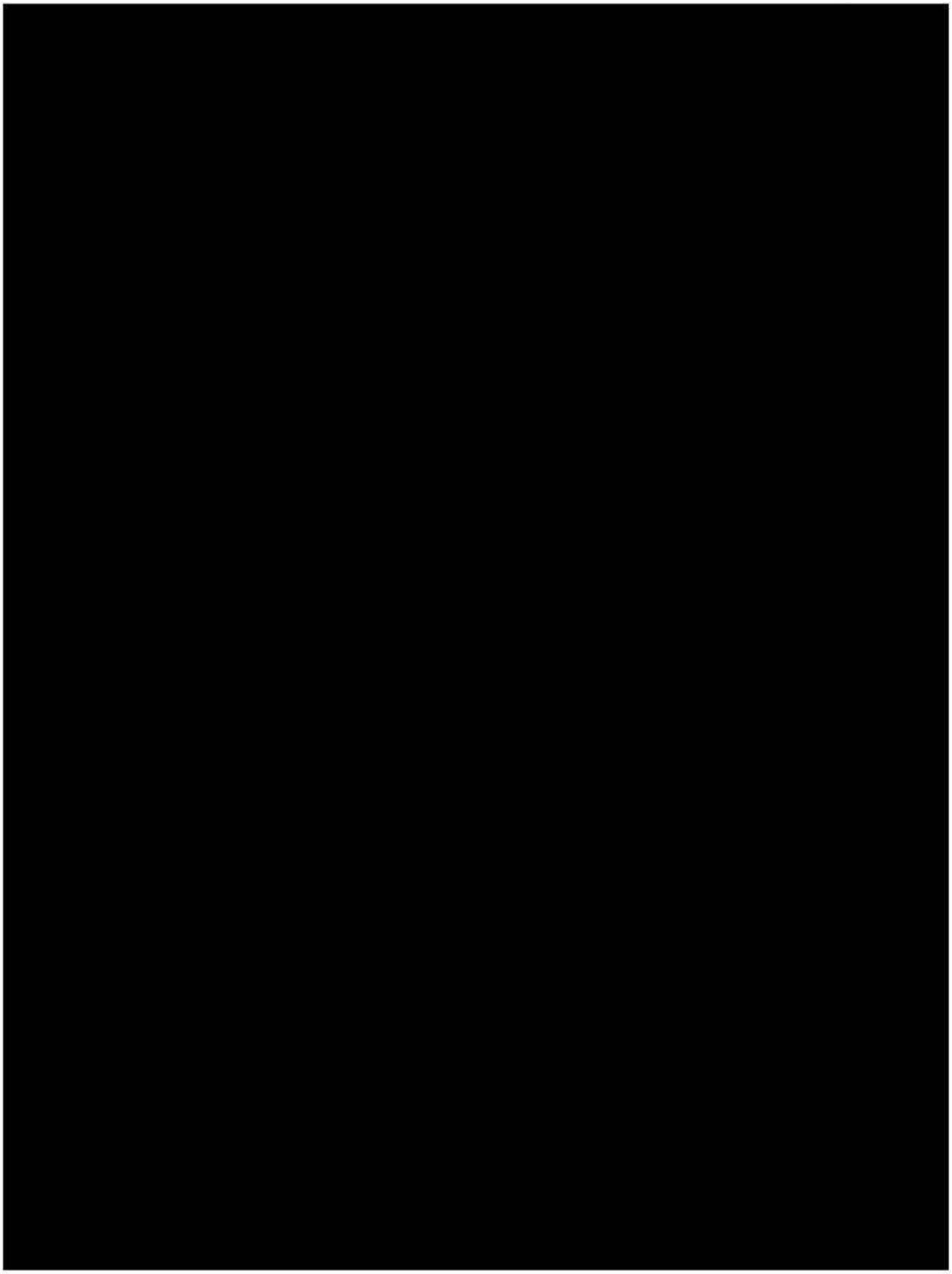
[redacted]

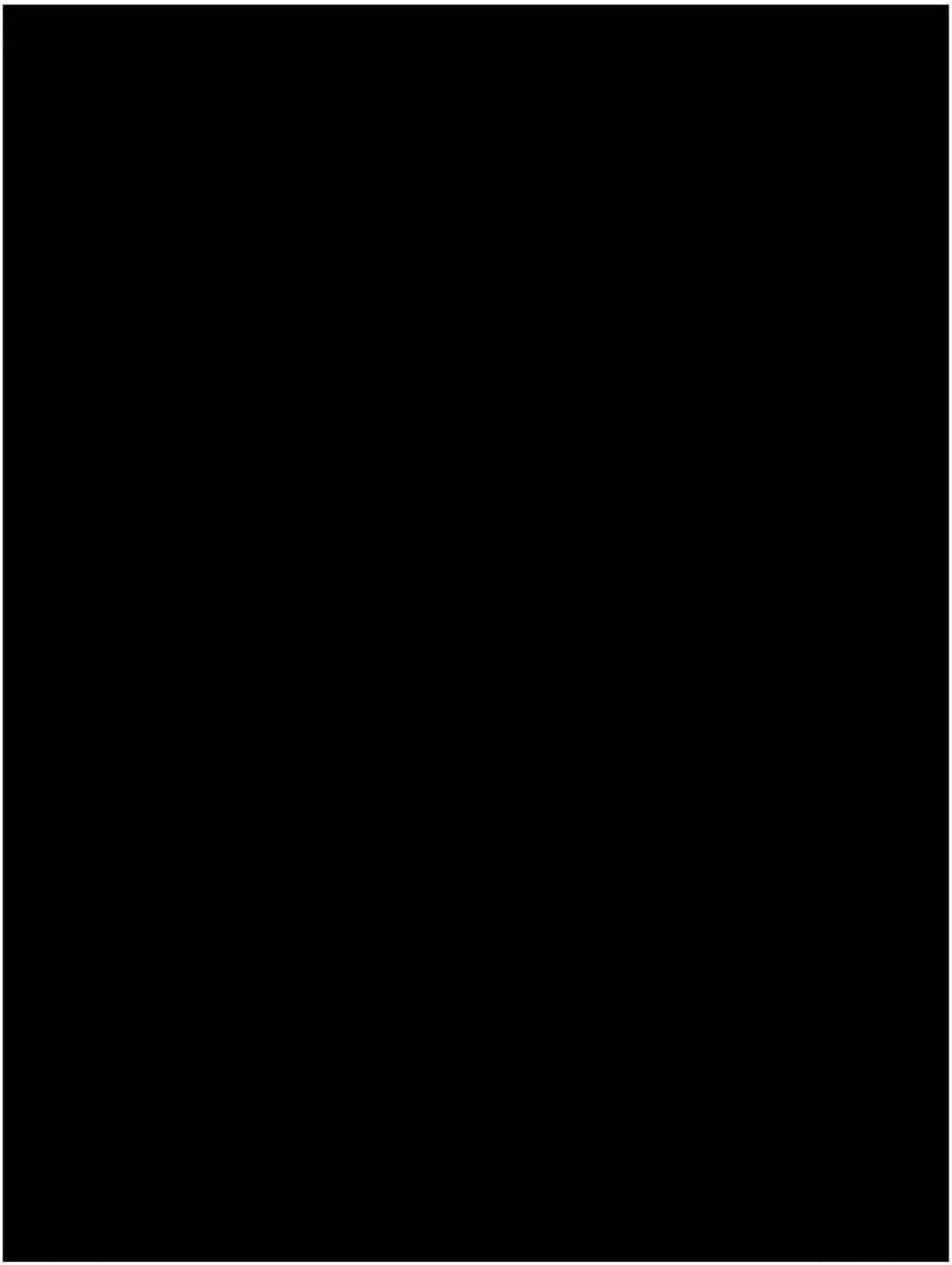
[redacted]

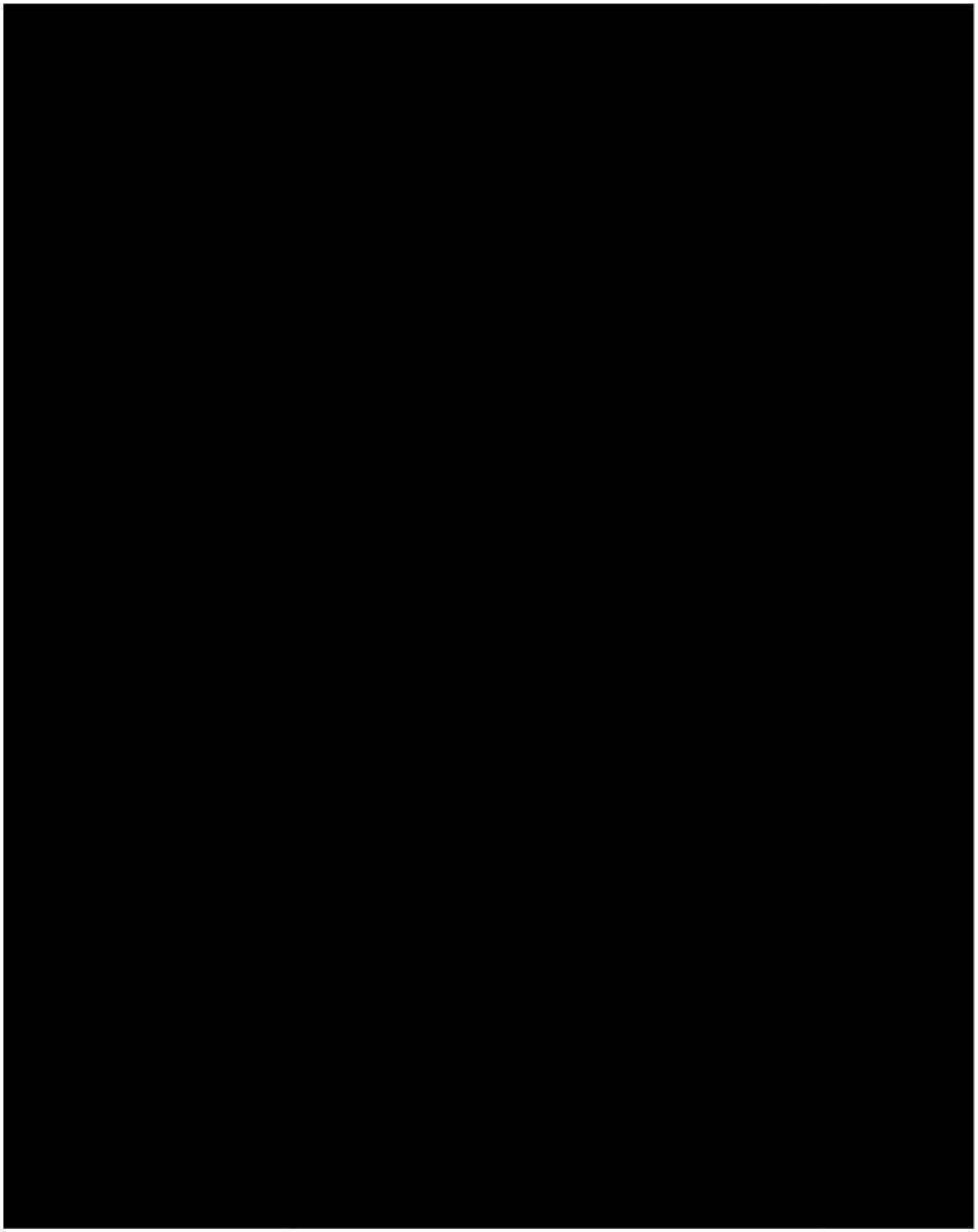
7 Appendix A: R Code

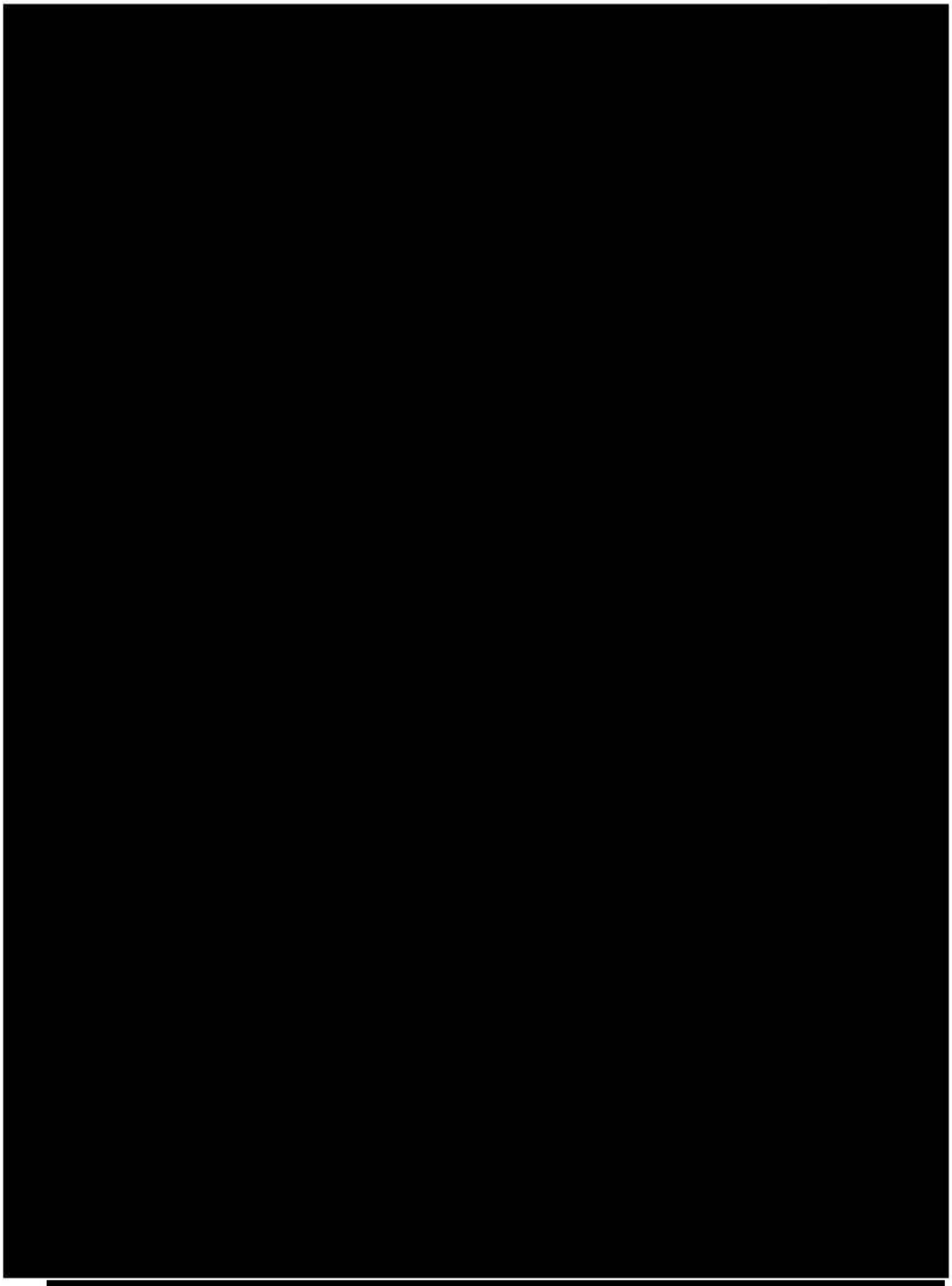
FUNCTION POWER.TSD.2 (FOR CALCULATING THE 'EMPIRIC' POWER OF TWO-STAGE BE STUDIES ACCORDING TO FDF MODIFIED POTVIN C DESIGN VIA SIMULATIONS)

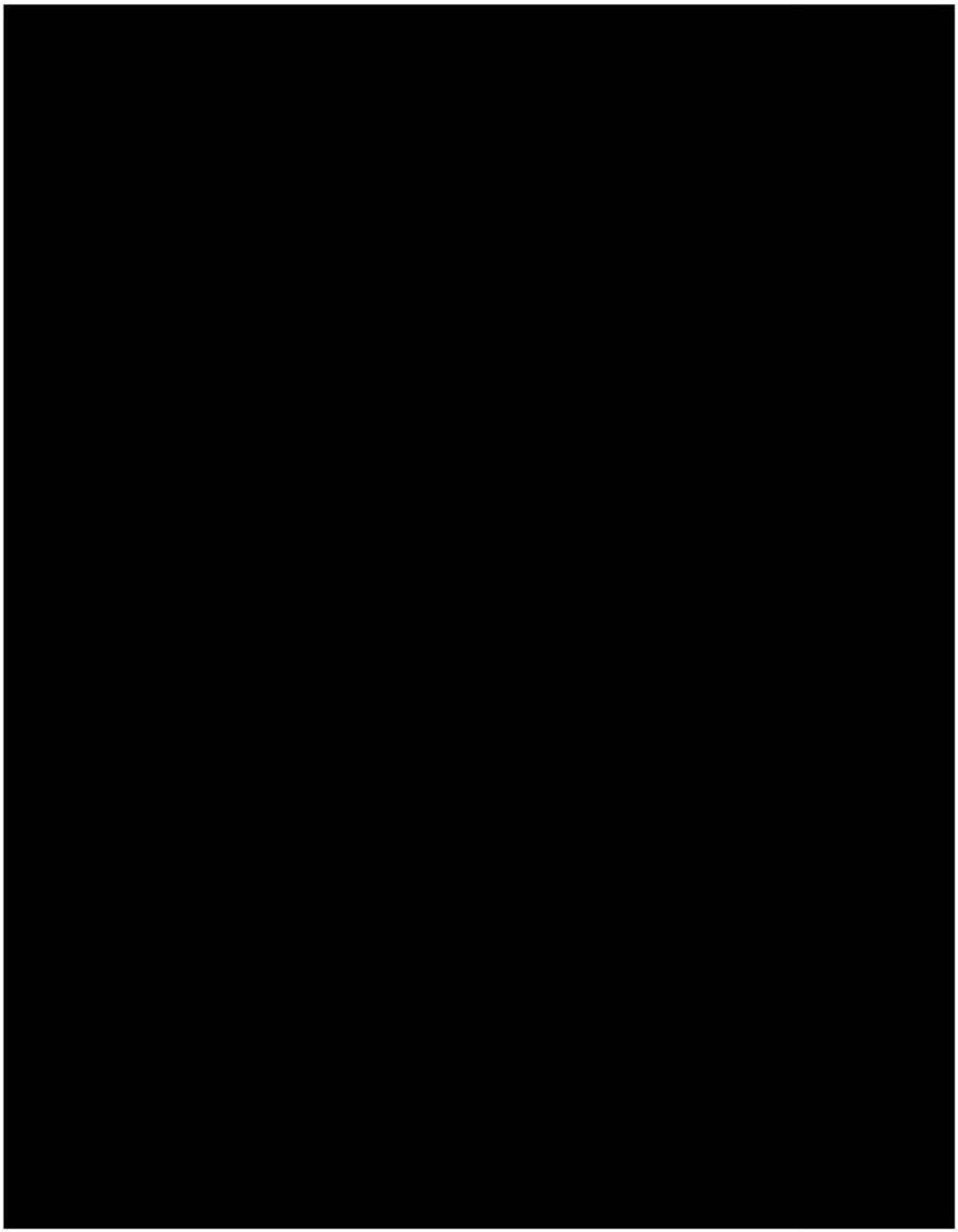
[redacted]

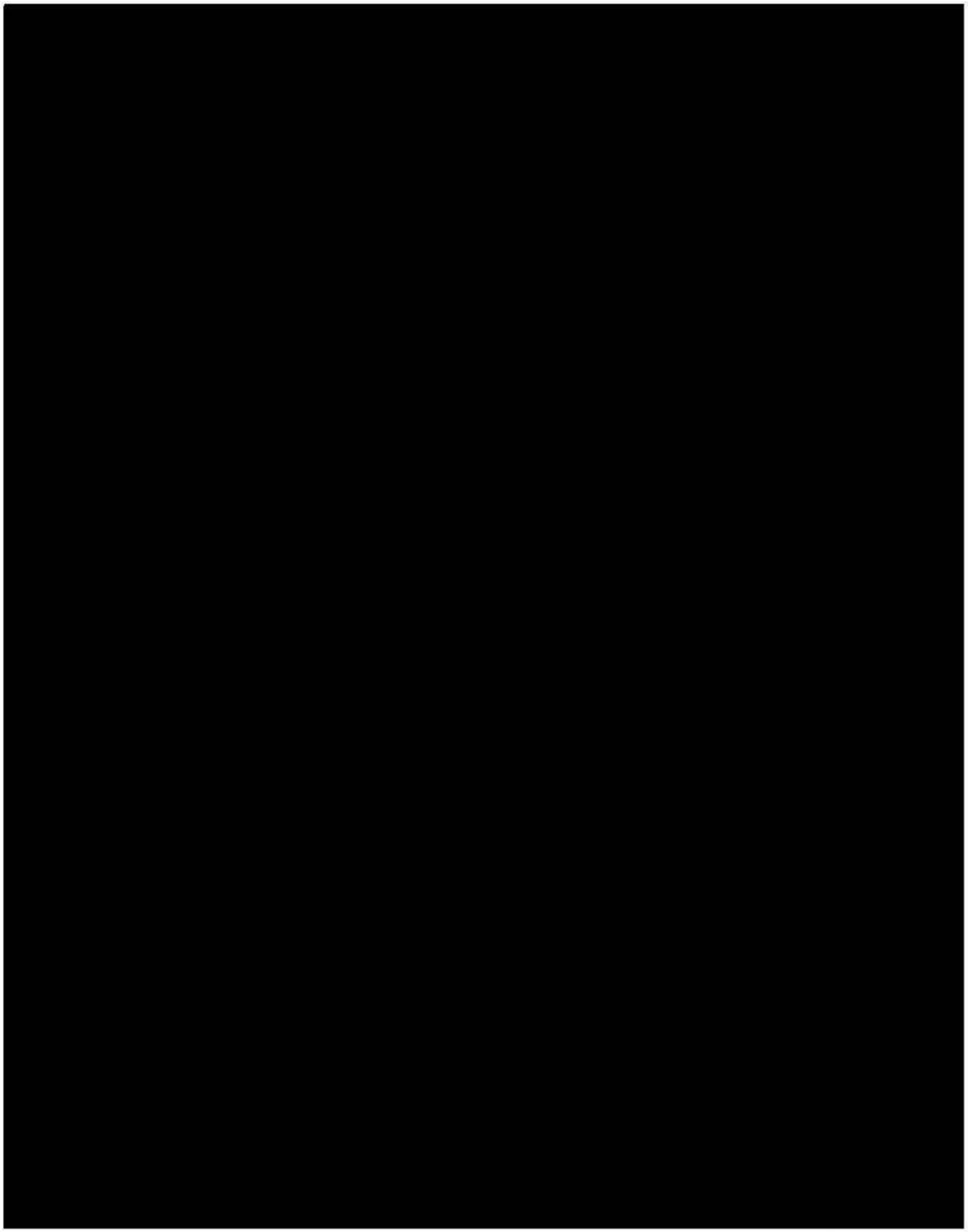


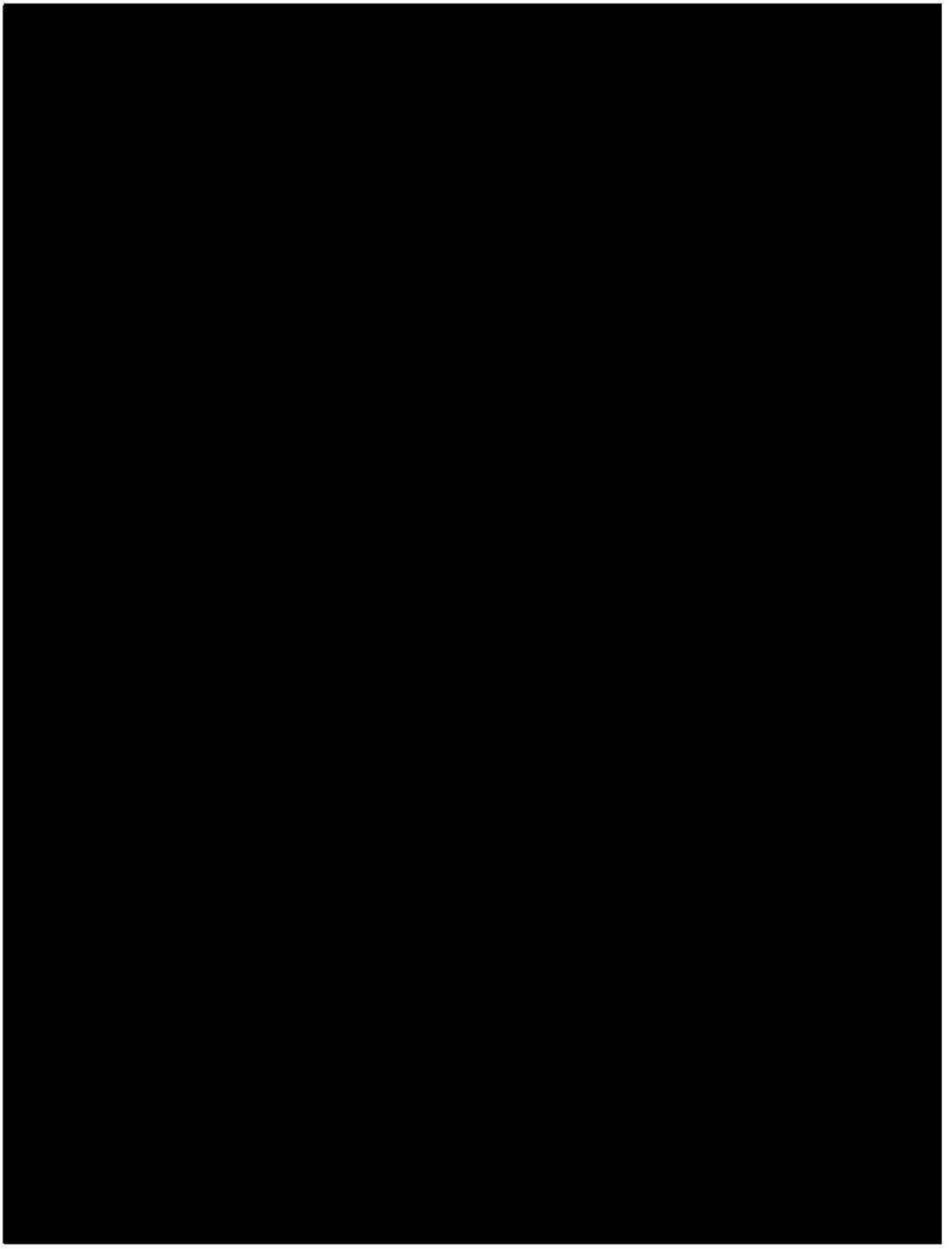


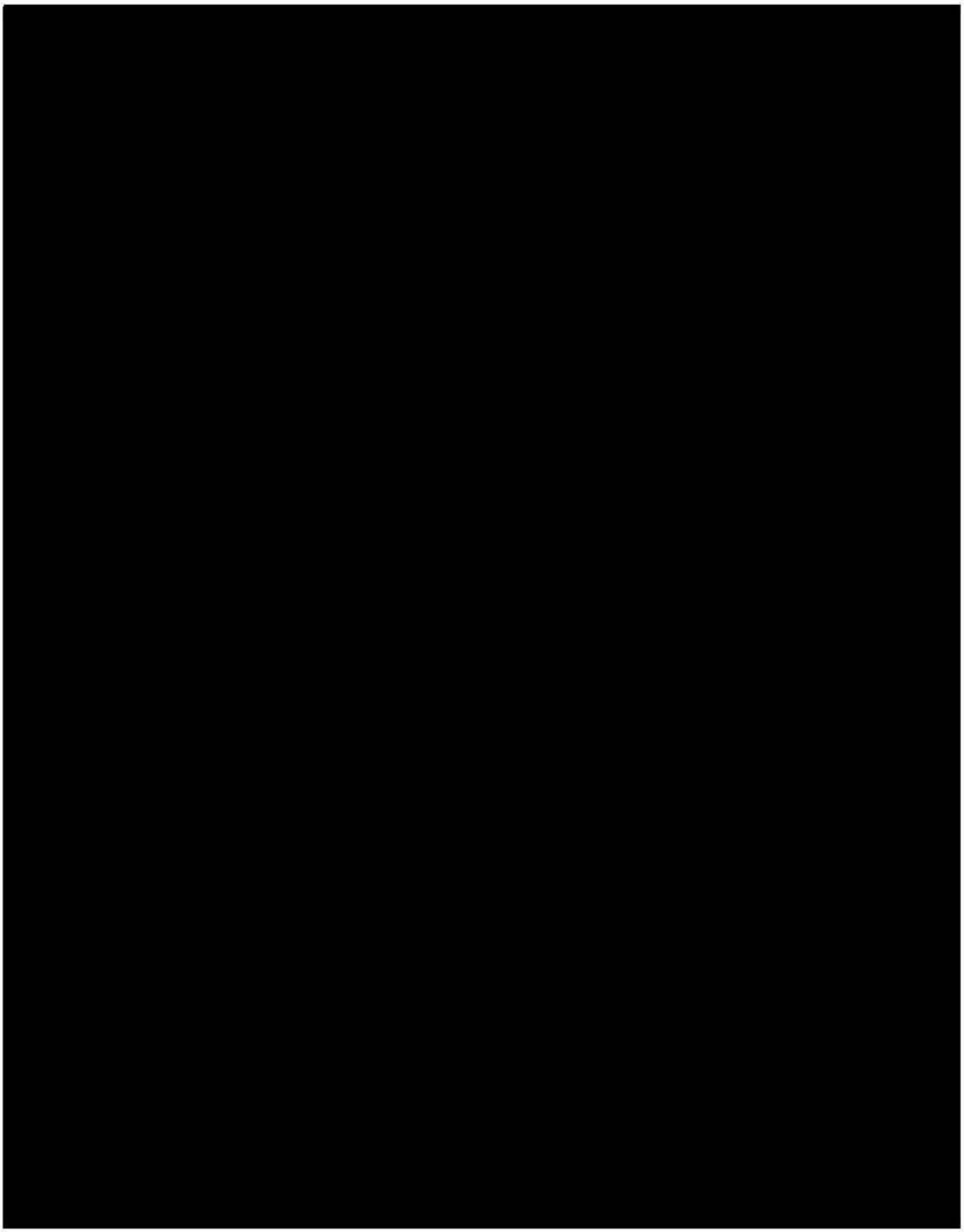


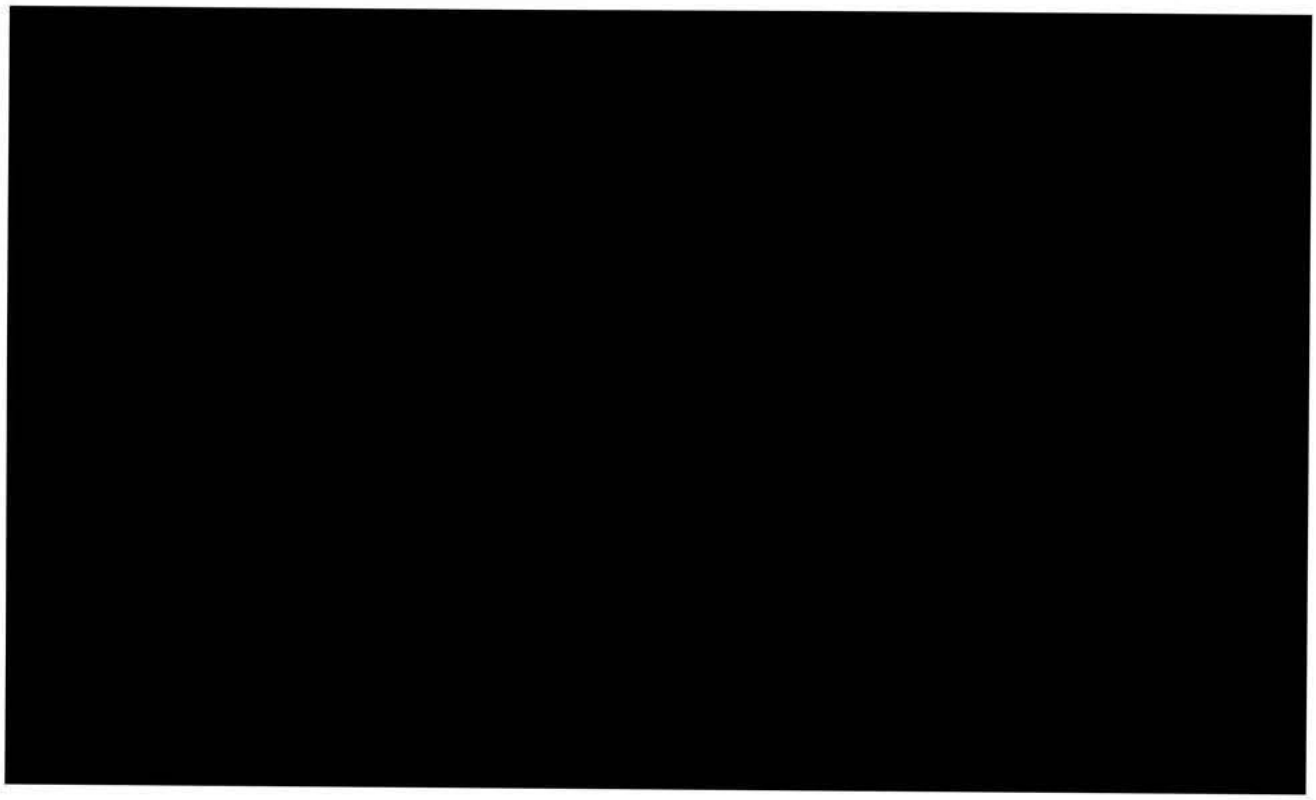












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8 Appendix B: The Evaluation of Operating Characteristics of the FDF modified Potvin Method C Design for the Maximal Total Sample Size of either [redacted]

Table B1. Estimated Type I Error (TIE) Rate of the FDF modified Potvin C Two-Stage Design (at Theta0 of 1.25 and Nmax of 150)

	n1 [redacted]							
CV								
20%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
22%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
24%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
26%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
28%	0.0498	0.0499	0.0499	0.0499	0.0499	0.0498	0.0499	0.0500
30%	0.0492	0.0497	0.0497	0.0497	0.0497	0.0497	0.0499	0.0500
32%	0.0483	0.0489	0.0491	0.0492	0.0494	0.0495	0.0498	0.0499
34%	0.0473	0.0480	0.0480	0.0482	0.0487	0.0489	0.0494	0.0496
36%	0.0465	0.0471	0.0474	0.0472	0.0477	0.0481	0.0485	0.0487
38%	0.0459	0.0465	0.0467	0.0463	0.0469	0.0470	0.0476	0.0480
40%	0.0462	0.0466	0.0460	0.0458	0.0464	0.0464	0.0468	0.0466

Table B2. Estimated Power of the FDF modified Potvin C Two-Stage Design (at Theta0 of 0.95 and Nmax of 150)

	n1 [redacted]							
CV								
20%	0.9939	0.9954	0.9963	0.9973	0.9979	0.9984	0.9987	0.9990
22%	0.9843	0.9871	0.9895	0.9915	0.9929	0.9943	0.9954	0.9964
24%	0.9673	0.9726	0.9771	0.9802	0.9837	0.9862	0.9883	0.9899
26%	0.9438	0.9511	0.9577	0.9632	0.9682	0.9727	0.9758	0.9793
28%	0.9157	0.9241	0.9327	0.9400	0.9462	0.9524	0.9577	0.9628
30%	0.8877	0.8958	0.9045	0.9133	0.9203	0.9273	0.9348	0.9410
32%	0.8635	0.8715	0.8781	0.8849	0.8936	0.9012	0.9096	0.9168

[redacted]

[redacted]

	n1 [redacted]							
34%	0.8449	0.8523	0.8569	0.8623	0.8709	0.8764	0.8845	0.8916
36%	0.8359	0.8422	0.8411	0.8455	0.8522	0.8558	0.8625	0.8663
38%	0.8294	0.8348	0.8358	0.8370	0.8387	0.8421	0.8458	0.8500
40%	0.8210	0.8253	0.8294	0.8318	0.8335	0.8371	0.8369	0.8379

Table B3. Estimated Type I Error (TIE) Rate of the FDF modified Potvin C Two-Stage Design (at Theta0 of 1.25 and Nmax of 200)

	n1 [redacted]							
CV								
20%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
22%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
24%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
26%	0.0499	0.0500	0.0499	0.0500	0.0499	0.0498	0.0499	0.0500
28%	0.0498	0.0499	0.0499	0.0499	0.0499	0.0498	0.0499	0.0500
30%	0.0492	0.0497	0.0497	0.0497	0.0497	0.0497	0.0499	0.0500
32%	0.0483	0.0489	0.0491	0.0492	0.0494	0.0495	0.0498	0.0499
34%	0.0473	0.0480	0.0480	0.0482	0.0487	0.0489	0.0494	0.0496
36%	0.0464	0.0470	0.0474	0.0473	0.0477	0.0482	0.0485	0.0487
38%	0.0460	0.0467	0.0466	0.0463	0.0468	0.0471	0.0474	0.0478
40%	0.0461	0.0467	0.0460	0.0458	0.0464	0.0465	0.0467	0.0466

Table B4. Estimated Power of the FDF modified Potvin C Two-Stage Design (at Theta0 of 0.95 and Nmax of 200)

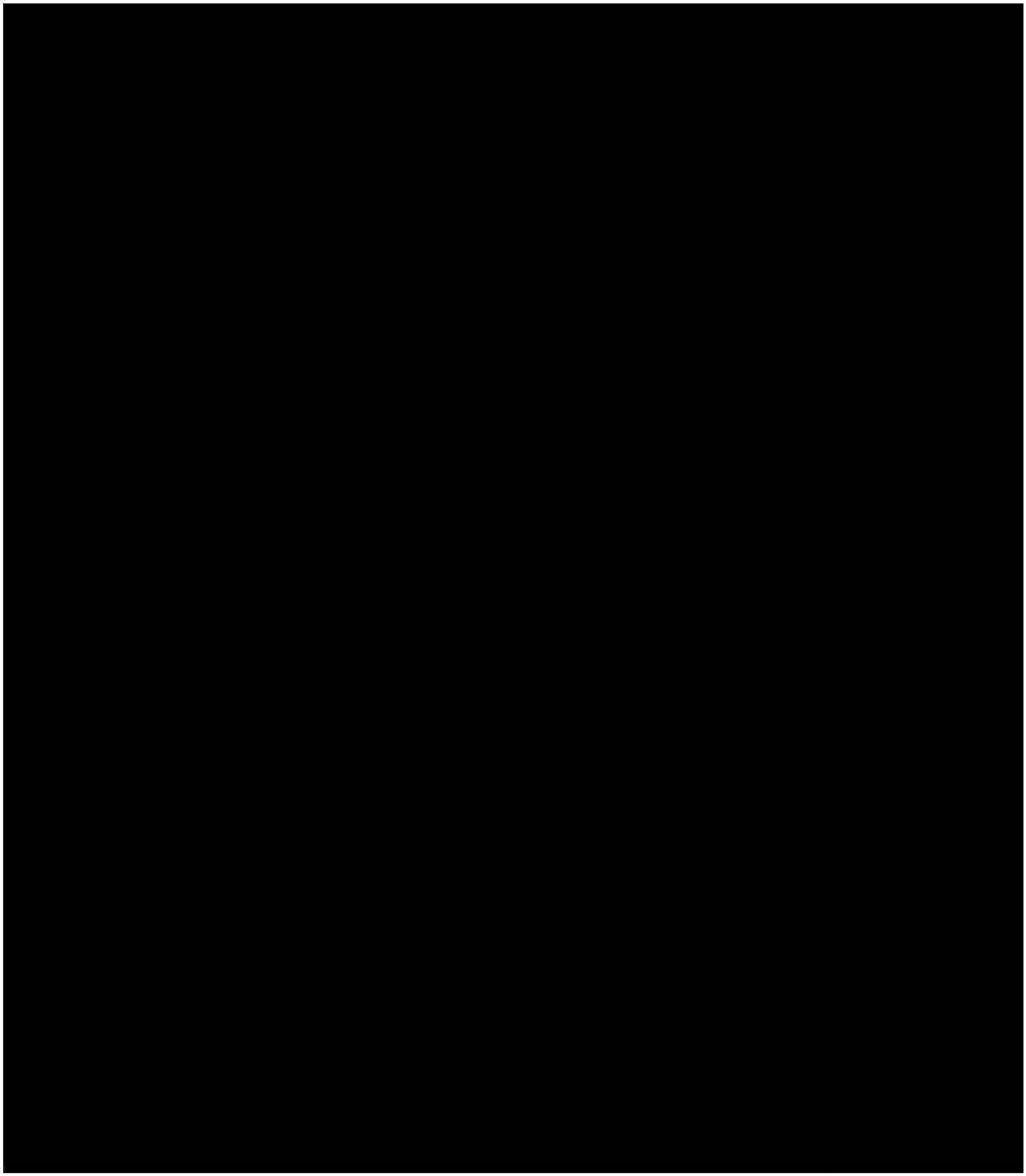
	n1 [redacted]							
CV								
20%	0.9939	0.9954	0.9963	0.9973	0.9979	0.9984	0.9987	0.9990
22%	0.9843	0.9871	0.9895	0.9915	0.9929	0.9943	0.9954	0.9964
24%	0.9673	0.9726	0.9771	0.9802	0.9837	0.9862	0.9883	0.9899
26%	0.9438	0.9511	0.9577	0.9632	0.9682	0.9727	0.9758	0.9793
28%	0.9157	0.9241	0.9327	0.9400	0.9462	0.9524	0.9577	0.9628

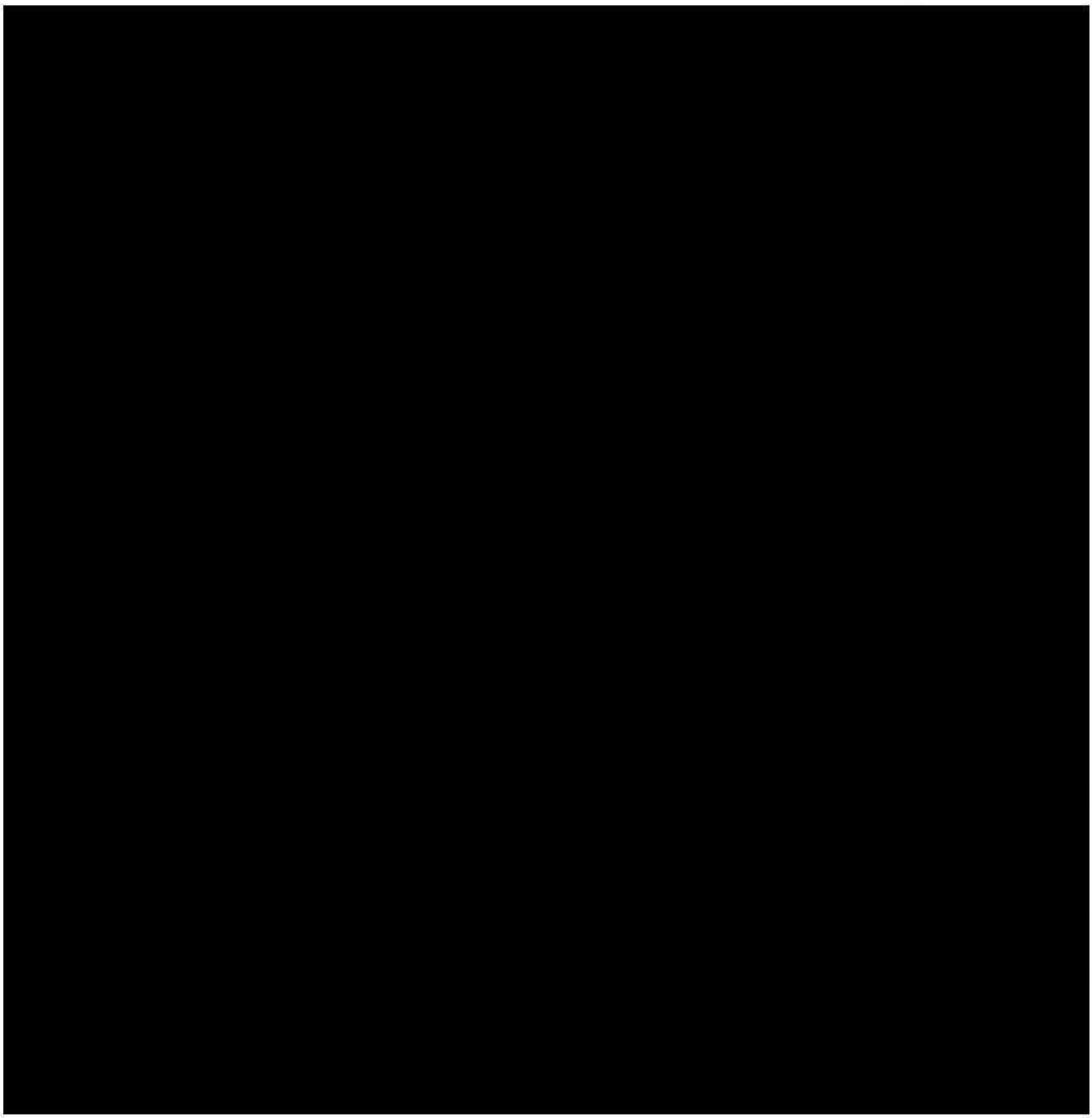
[redacted]

[redacted]

	n1 [redacted]							
30%	0.8877	0.8958	0.9045	0.9133	0.9203	0.9273	0.9348	0.9410
32%	0.8635	0.8715	0.8781	0.8849	0.8936	0.9012	0.9096	0.9168
34%	0.8449	0.8523	0.8569	0.8623	0.8709	0.8764	0.8845	0.8916
36%	0.8359	0.8422	0.8411	0.8455	0.8522	0.8558	0.8625	0.8663
38%	0.8292	0.8339	0.8358	0.8371	0.8382	0.8421	0.8458	0.8500
40%	0.8222	0.8259	0.8298	0.8314	0.8337	0.8361	0.8369	0.8378

[redacted]





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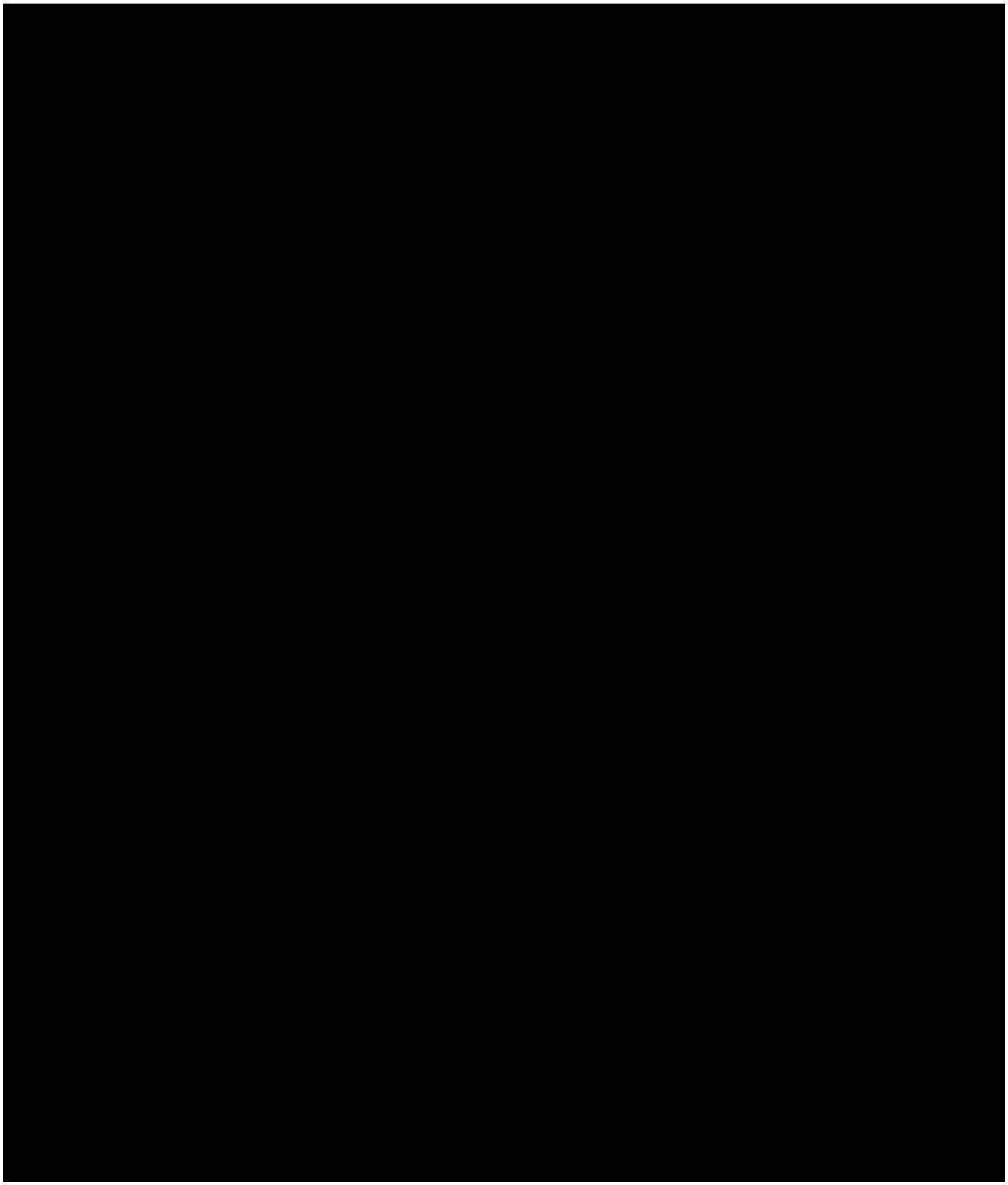

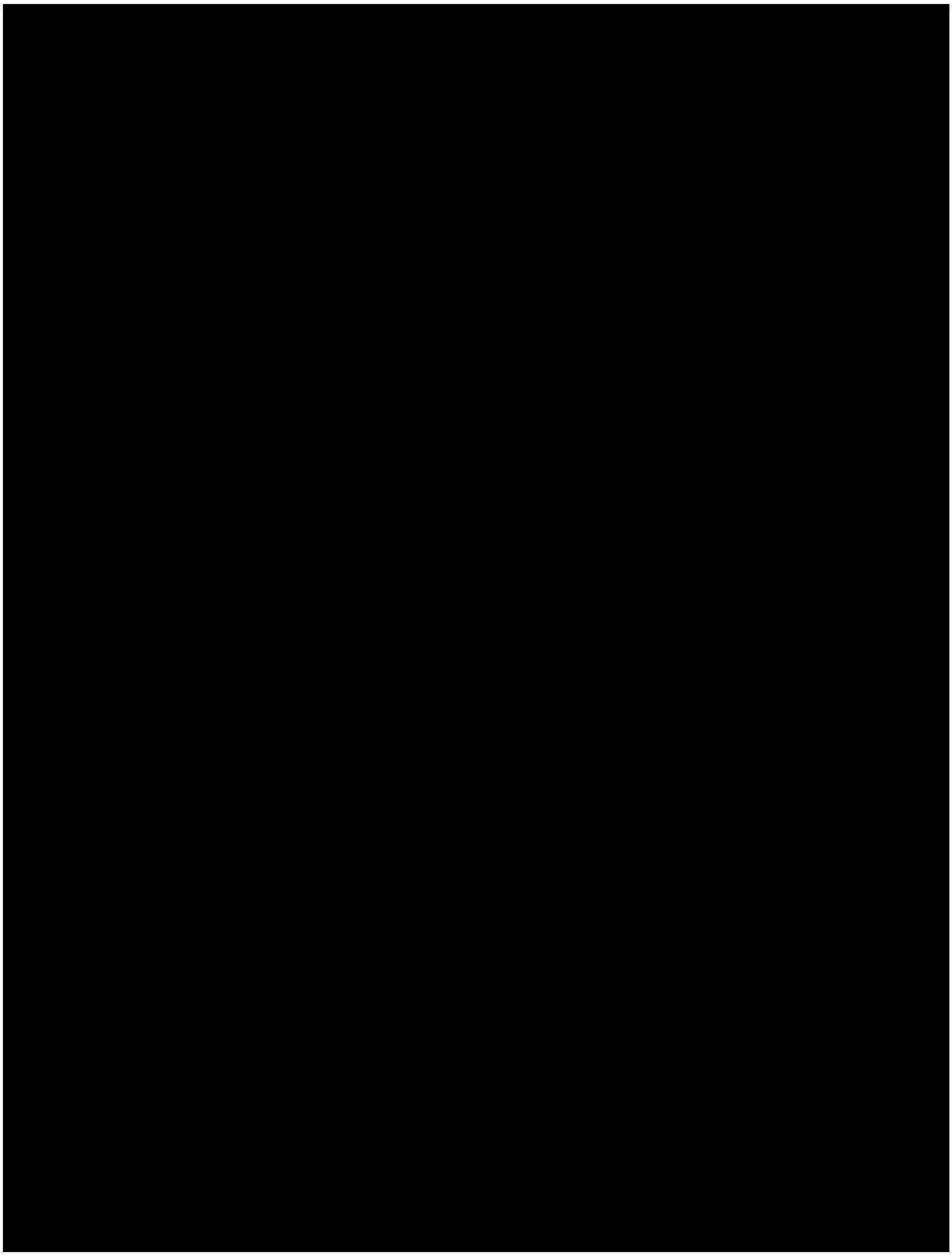

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Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact [redacted] - Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: [redacted]

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify [redacted] - Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by [redacted] - Part 11 during the course of your relationship with [redacted] - Part 11.