Statistical Analysis Plan (SAP)

STUDY NUMBER(S): AIOA001

PROTOCOL(S) TITLE: A PHASE 2B, PROSPECTIVE, DOUBLE-BLINDED, RANDOMIZED CONTROLLED TRIAL OF THE MICRONIZED dHACM INJECTION AS COMPARED TO SALINE PLACEBO INJECTION IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE

NCT: 03485157

SAP DATE: 06/24/2020

16.1.9 DOCUMENTATION OF STATISTICAL METHODS

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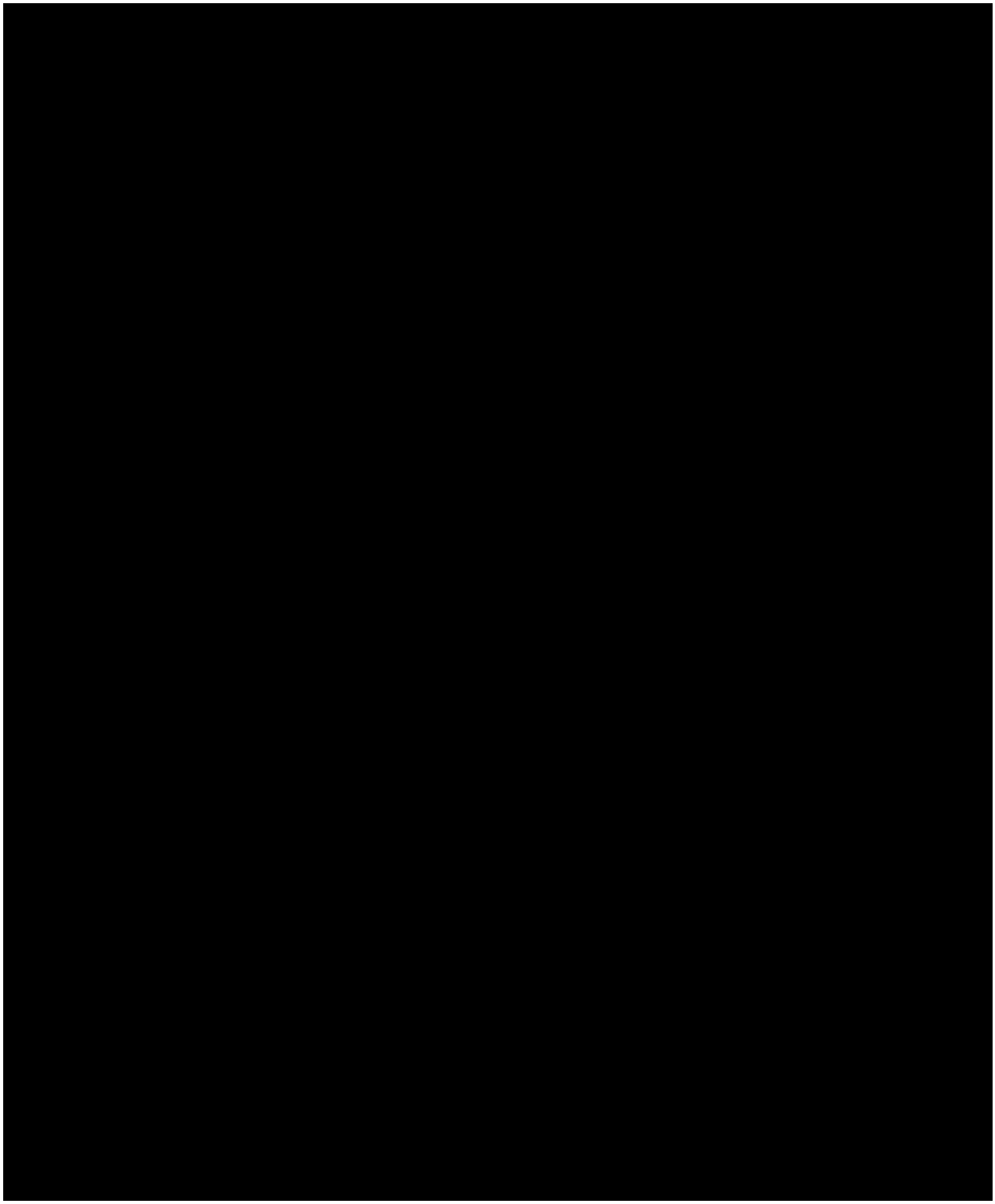

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This Statistical Analysis Plan (SAP) is intended to act as an outline for the statistical interpretation of the data resulting from the Phase 2B Investigational New Drug (IND) trial, titled: "A Phase 2B, Prospective, Double-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection as Compared to Saline Placebo Injection in the Treatment of Osteoarthritis of the Knee." Specific questions regarding this trial's design and/or implementation may be addressed by the study protocol (AIOA001 Protocol V2).

This study consists of two phases – Main Phase and Open-Label Extension Phase (Extension Phase). The Main Phase of the study includes subjects during the observation period where they received the randomized treatment only. The Extension Phase of the study includes the subjects who elected to receive an open-label injection of micronized dHACM injection at either of the 180-day, 270-day or 365-day visits, during the 180-day period following the open-label injection.

In order to facilitate the planning of a Phase 3 pivotal study based on results of the primary and secondary efficacy parameters at 90-day and 180-day, the randomized treatment for the Main Phase will be unblinded and a snapshot of the database will be taken after all randomized subjects completed the 180-day assessment. Formal database preparation process will be performed to ensure the integrity and quality of the database and an interim analysis of the primary and secondary efficacy endpoints as well as the exploratory efficacy endpoints up to the 180-day time point will be performed. At the end of the study, the database will be locked. The database lock process will be performed to ensure the integrity and quality of the database; and formal analyses will be performed.

1 STUDY OBJECTIVES

This Phase 2B IND Trial will be conducted to determine the safety and effectiveness of micronized dehydrated Human Amnion/Chorion Membrane (dHACM) as compared to the 0.9% sodium chloride, USP placebo control for the treatment of osteoarthritis of the knee.

2 PRIMARY OBJECTIVES

The primary objective of this study is to determine the effectiveness of pain reduction and improvement of function after being treated with micronized dHACM as compared to the 0.9% sodium chloride, USP placebo control in patients with osteoarthritis of the knee.

2.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are as follows:

- Change in Visual Analog Scale (VAS) score for pain between baseline and 90 days

- Change in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index total score (Total WOMAC score), between baseline and 90 days

2.1.1 VAS for Pain

The VAS for pain[1] is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with rheumatic diseases. The VAS for pain is a continuous scale comprised of a horizontal visual analog scale, usually 10 centimeters (100 mm) in length, and is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 [100-mm scale]).

2.1.2 Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index

The Western Ontario and McMaster Universities (WOMAC) osteoarthritis index[2] is a validated, self-administered instrument developed in 1982 to evaluate a patient's disability as it relates to arthritis in the knee. The WOMAC index evaluates the level of disability due to osteoarthritis using 24 questions that comprise three subscales: pain, stiffness, and function. The Total WOMAC score is calculated as the sum of each item which is on a 0 to 4 point scale. The items total to a maximum of 96 points with a higher score indicating greater disability.

Should a patient fail to complete all items within a single questionnaire, missing data will be handled utilizing recommendations provided within the WOMAC User Guide[2], which states:

"If ≥ two pain, both stiffness, or ≥ four physical function items are omitted, the patient's response is regarded as invalid and the deficient subscale(s) should not be used in the analysis. Where one pain, one stiffness, or 1-3 physical function items are missing, we suggest substituting the average value for the subscale in lieu of the missing item value(s)."

2.2 Primary Safety Endpoint

The primary safety endpoint is the proportion of product-related Adverse Events (AEs), Serious Adverse Events (SAEs), and unanticipated adverse events throughout the study.

3 SECONDARY OBJECTIVES

The secondary objectives of this study are to determine the longer-term effectiveness of pain reduction and level of disability after being treated with micronized dHACM as compared to the 0.9% sodium chloride, USP placebo control in patients with osteoarthritis of the knee.

3.1 Secondary Efficacy Endpoints

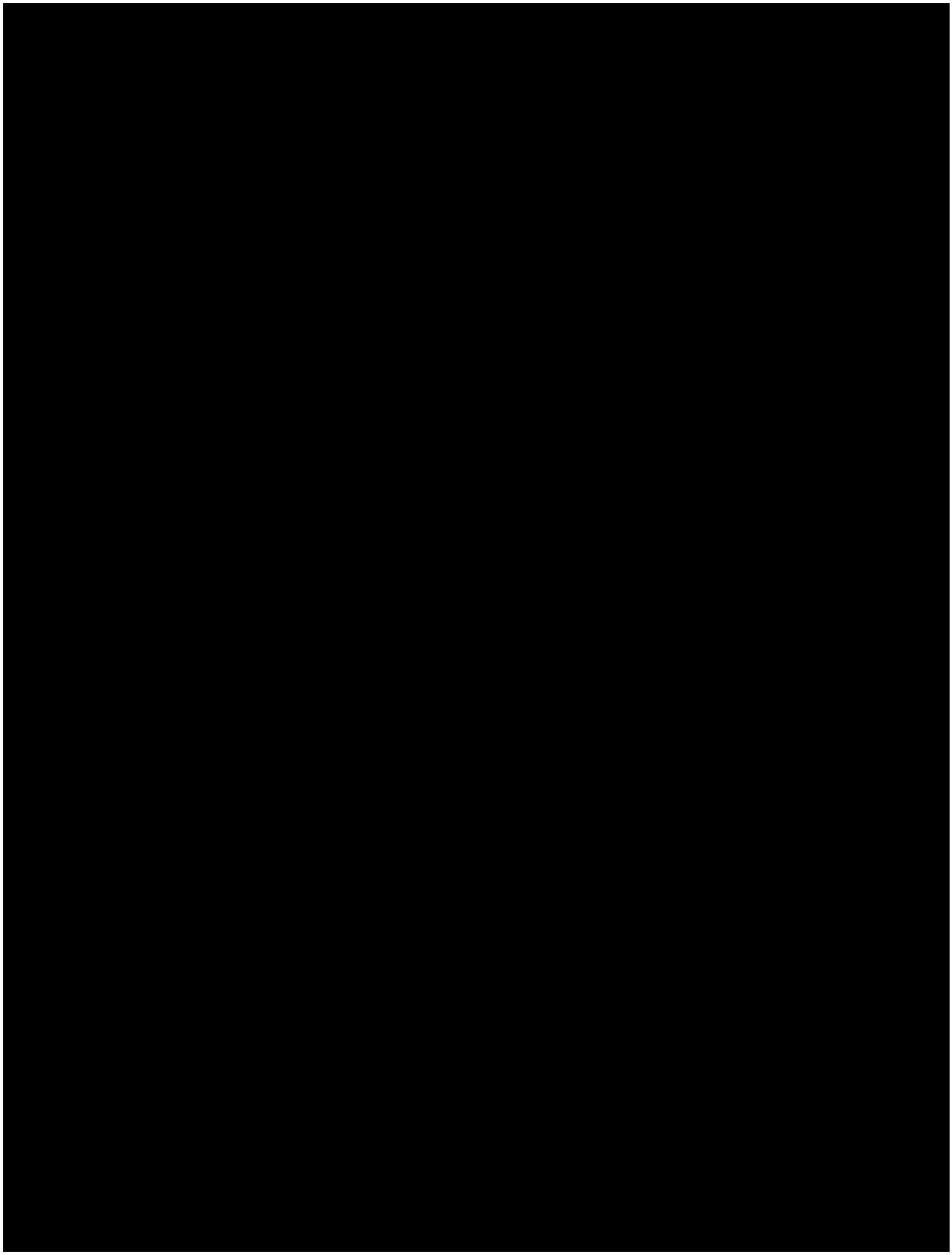
The secondary efficacy endpoints are as follows:

- Change in VAS score for pain between baseline and 180 days
- Change in Total WOMAC score between baseline and 180 days

4 EXPLORATORY OBJECTIVES

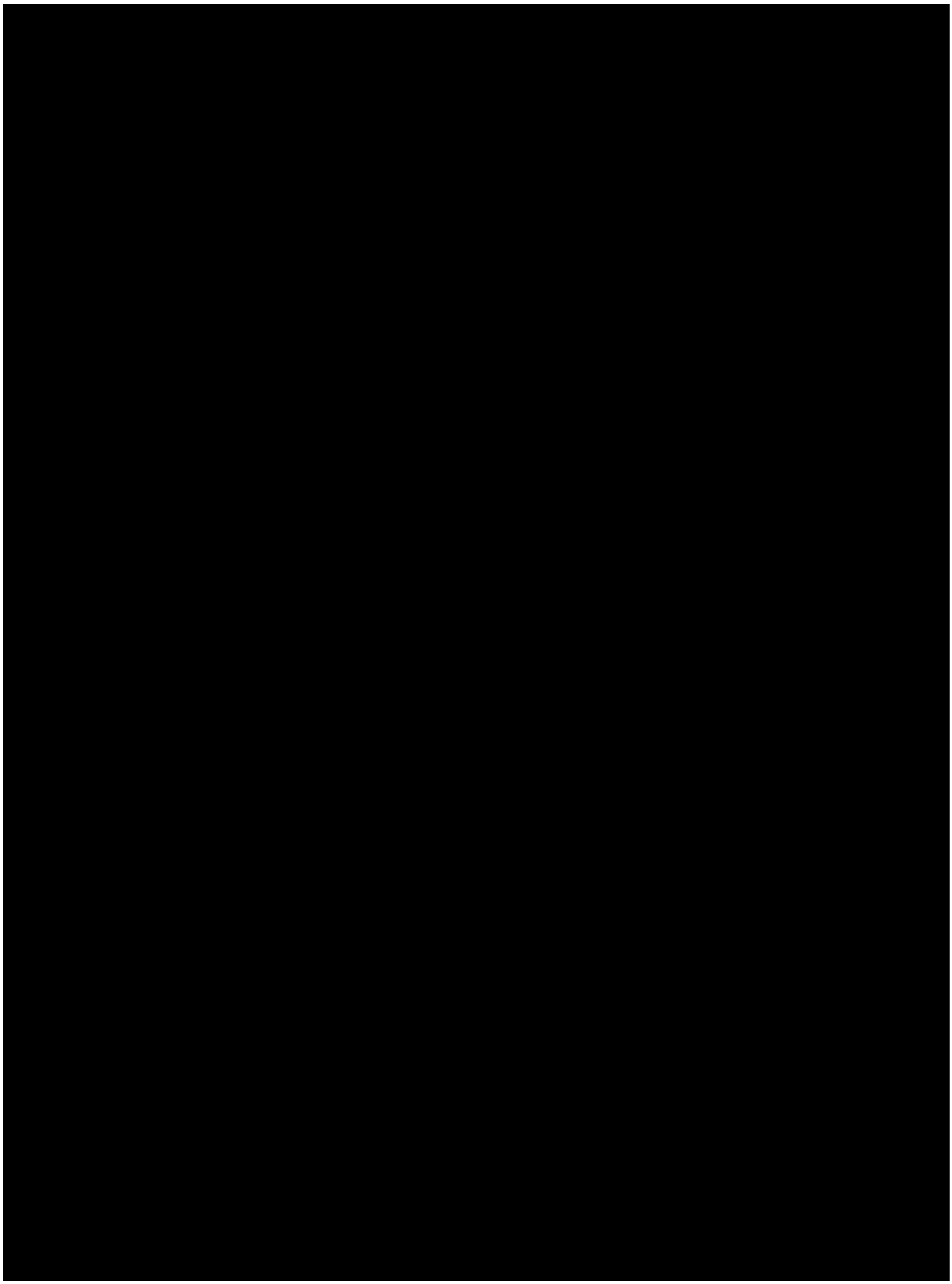
The exploratory objectives of this study are intended to assess further the effectiveness in pain reduction and level of disability after being treated with micronized dHACM as compared to the 0.9% sodium chloride, USP placebo control in patients with osteoarthritis of the knee, throughout the course of the study.

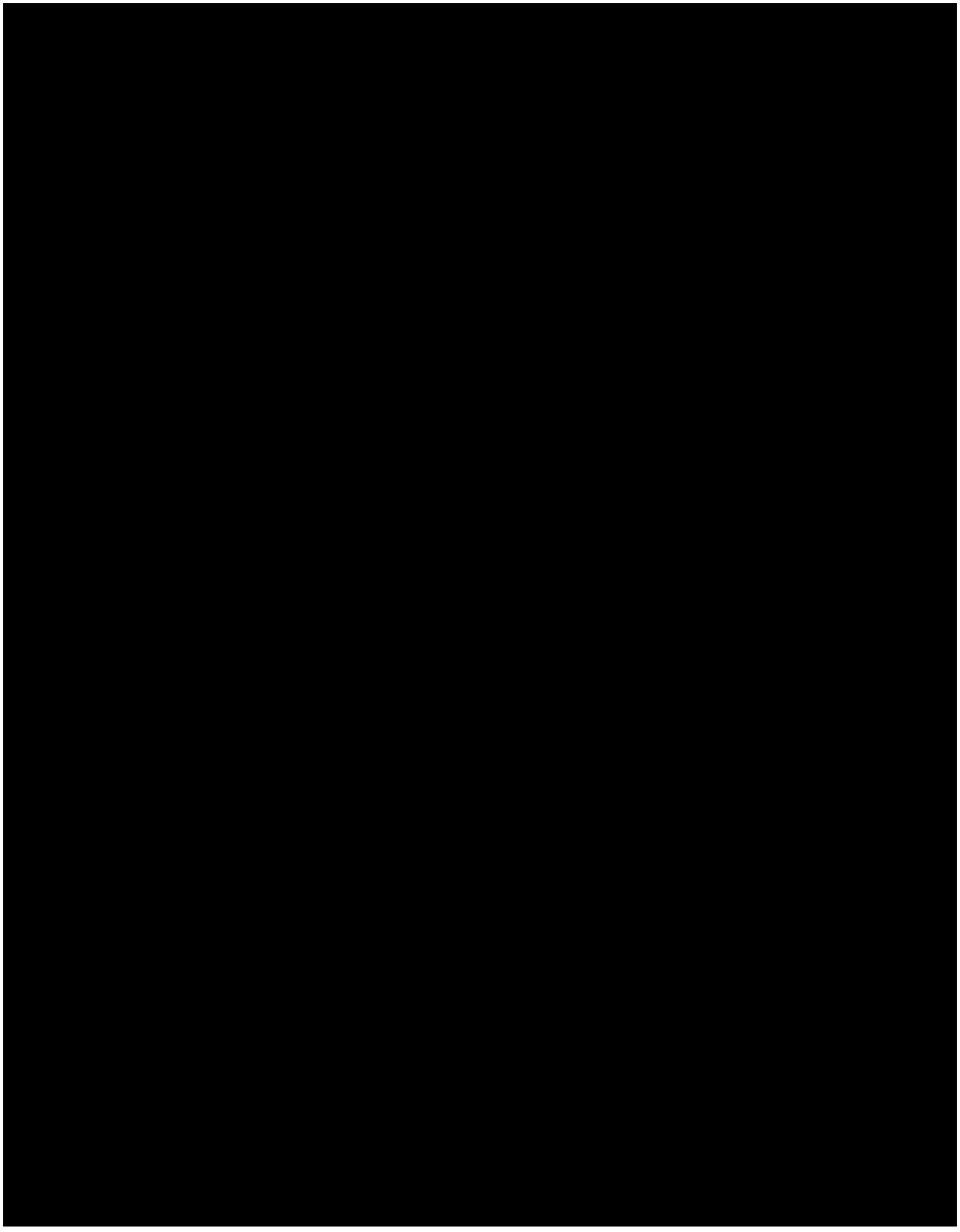
As outlined in AIOA001 protocol, all study subjects will become eligible to receive an open-label injection of micronized dHACM at either of the 180-day, 270-day, or 365-day time points. Due to this change in treatment from the original protocol, all endpoints following the 180-day time point become exploratory objectives.

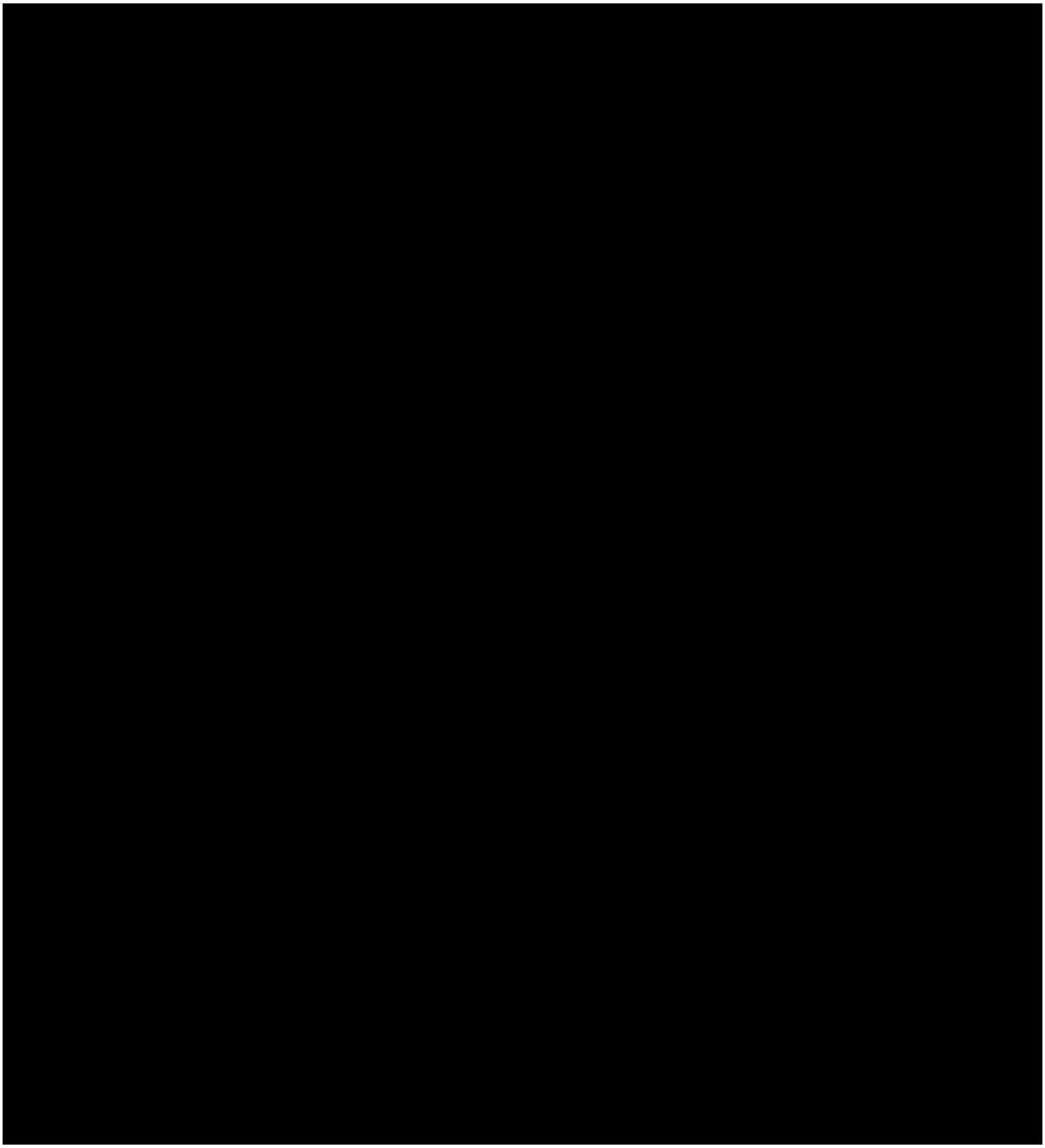


5 STUDY SUCCESS CRITERIA

6 STUDY DESIGN AND PLAN







7 STATISTICAL METHODS

7.1 Statistical and Analytical Plans

7.1.1 General Considerations

For the purposes of this protocol, osteoarthritis of the knee outcomes will be examined. The hypothesis to be tested is to confirm that the use of micronized dHACM offers a

statistically significant advantage over 0.9% normal saline solution placebo for the treatment of osteoarthritis of the knee.

All statistical tests will be two-sided and will be performed at the [redacted] level of significance, unless otherwise stated. Note that a [redacted] penalty will be applied due to performing 2 planned interim analyses (see Section 7.1.11 for more details). Continuous data will be summarized by randomized Active and Control groups using descriptive statistics (number, mean, median, standard deviation [SD], minimum, and maximum). Categorical data will be summarized by randomized Active and Control groups using frequency tables (frequencies and percentages).

In addition to the efficacy analyses at the time point specified in the primary, secondary, and exploratory efficacy analyses, all efficacy parameters collected at various time points during the study will also be presented.

All analyses and summaries will be generated using SAS (SAS Institute, Inc., Cary, North Carolina).

7.1.2 Analysis Set

[redacted]

[redacted]

7.1.3 Co-Primary Efficacy Analysis

This study consists of co-primary efficacy endpoints, which requires both endpoints to demonstrate success at 2-sided, [redacted] level of significance.

7.1.3.1 VAS Score for Pain Analysis (90 Days)

[redacted]

ANOVA on the change in VAS score for pain between baseline and 90 days with treatment as a fixed effect and study site as the block effect will be used to compare the efficacy between Active and Control groups at 2-sided, [redacted] level of significance.

In the case of data not being normally distributed, nonparametric tests, such as Wilcoxon Rank Sum test, will be utilized to assess the treatment efficacy.

7.1.3.2 Total WOMAC Score Analysis (90 Days)

[redacted]

[redacted]

ANOVA on the change in Total WOMAC score between baseline and 90 days with treatment as a fixed effect and study site as the block effect will be used to compare the efficacy between Active and Control groups at 2-sided, [redacted] level of significance.

In the case of data not being normally distributed, nonparametric tests, such as Wilcoxon Rank Sum test, will be utilized to assess the treatment efficacy.

7.1.4 Secondary Efficacy Analysis

This study consists of two secondary efficacy endpoints that will be evaluated individually to demonstrate success at 2-sided, [redacted] level of significance. Success in either endpoint is intended to be used for future product claims.

7.1.4.1 VAS Score for Pain Analysis (180 Days)

[redacted]

ANOVA on the change in VAS score for pain between baseline and 180 days with treatment as a fixed effect and study site as the block effect will be used to compare the efficacy between Active and Control groups at 2-sided, [redacted] level of significance.

In the case of data not being normally distributed, nonparametric tests, such as Wilcoxon Rank Sum test, will be utilized to assess the treatment efficacy.

7.1.4.2 Total WOMAC Score Analysis (180 Days)

[redacted]

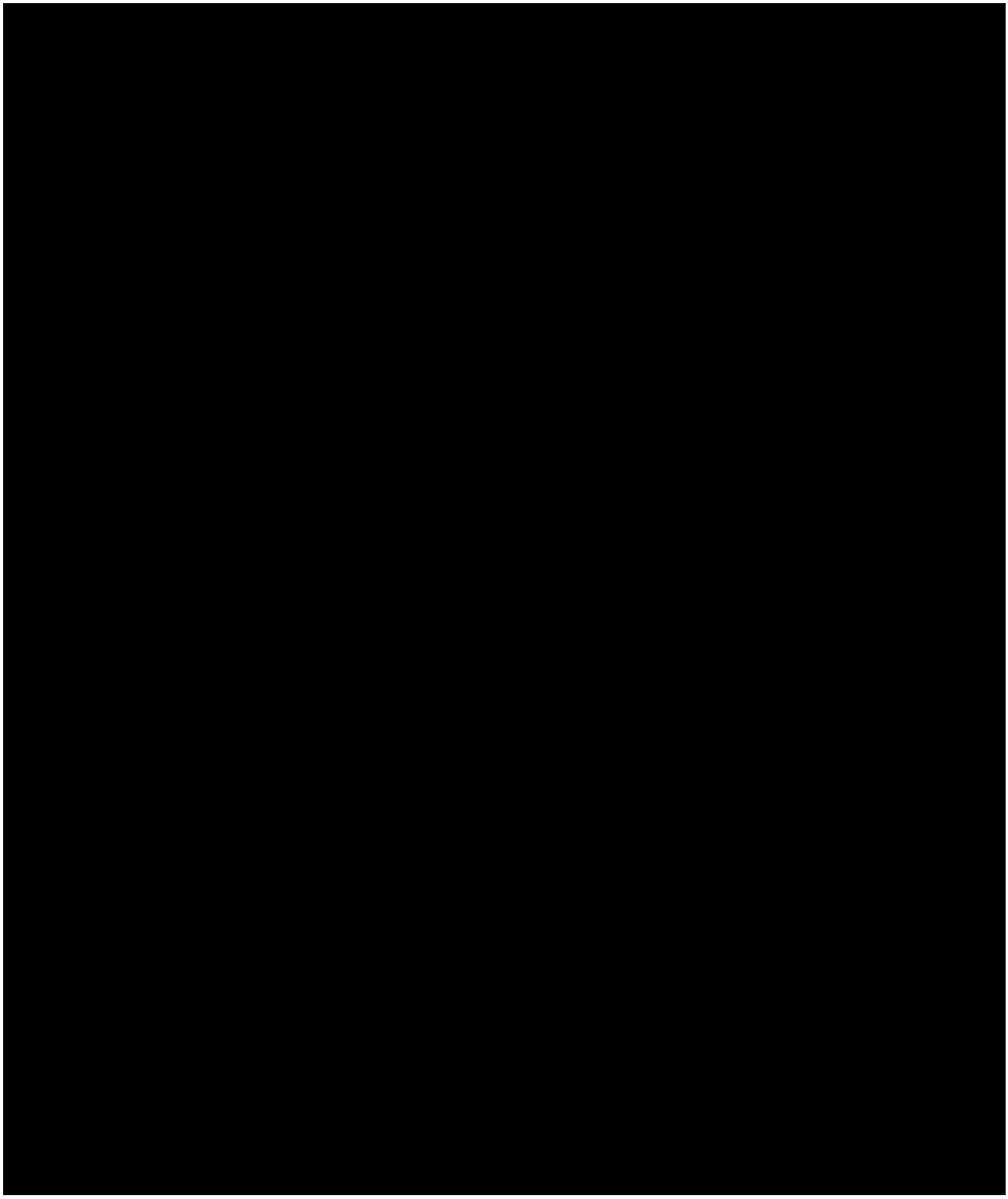
[redacted]

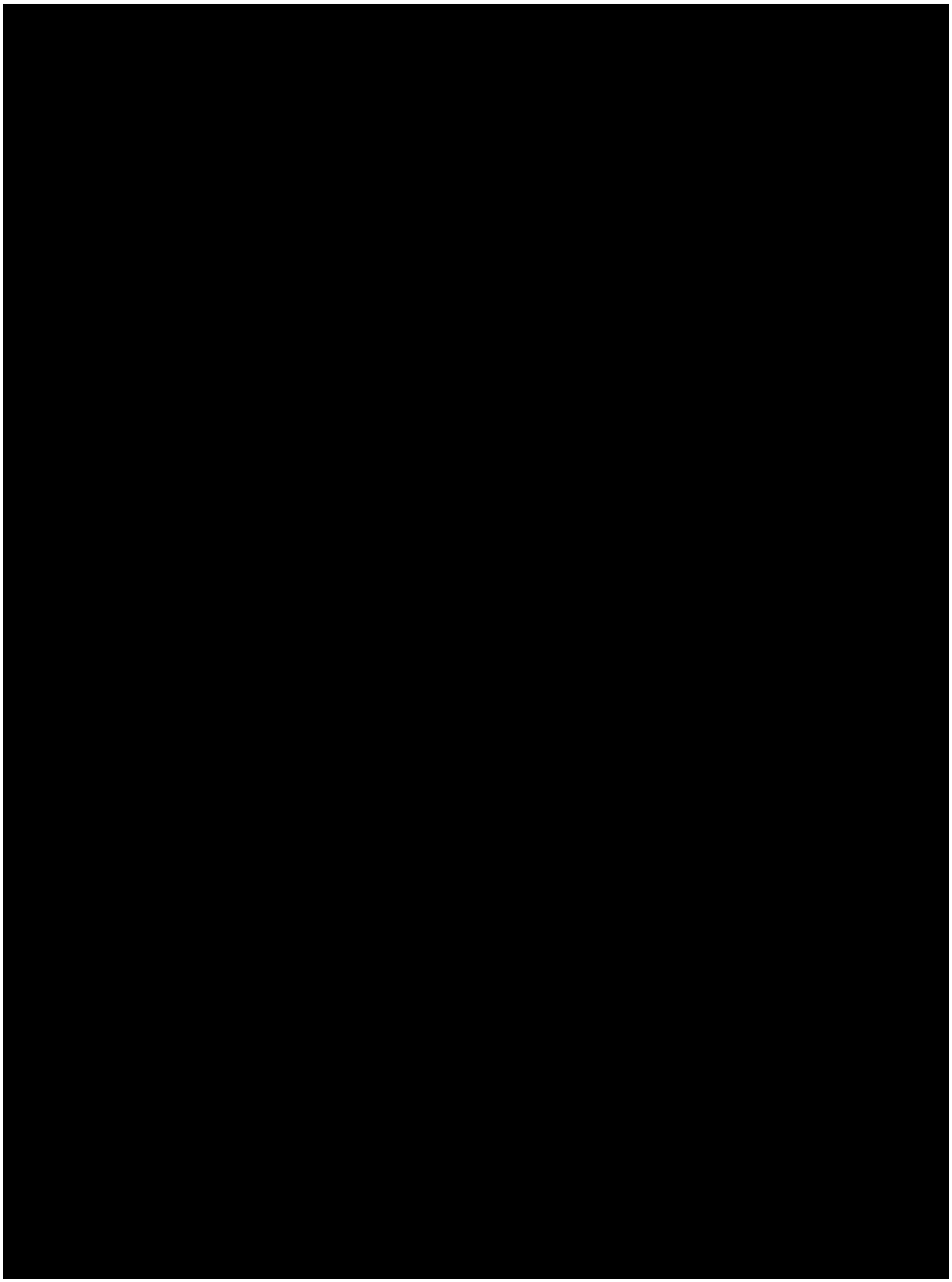
ANOVA on the change in Total WOMAC score between baseline and 180 days with treatment as a fixed effect and study site as the block effect will be used to compare the efficacy between Active and Control groups at 2-sided, [redacted] level of significance.

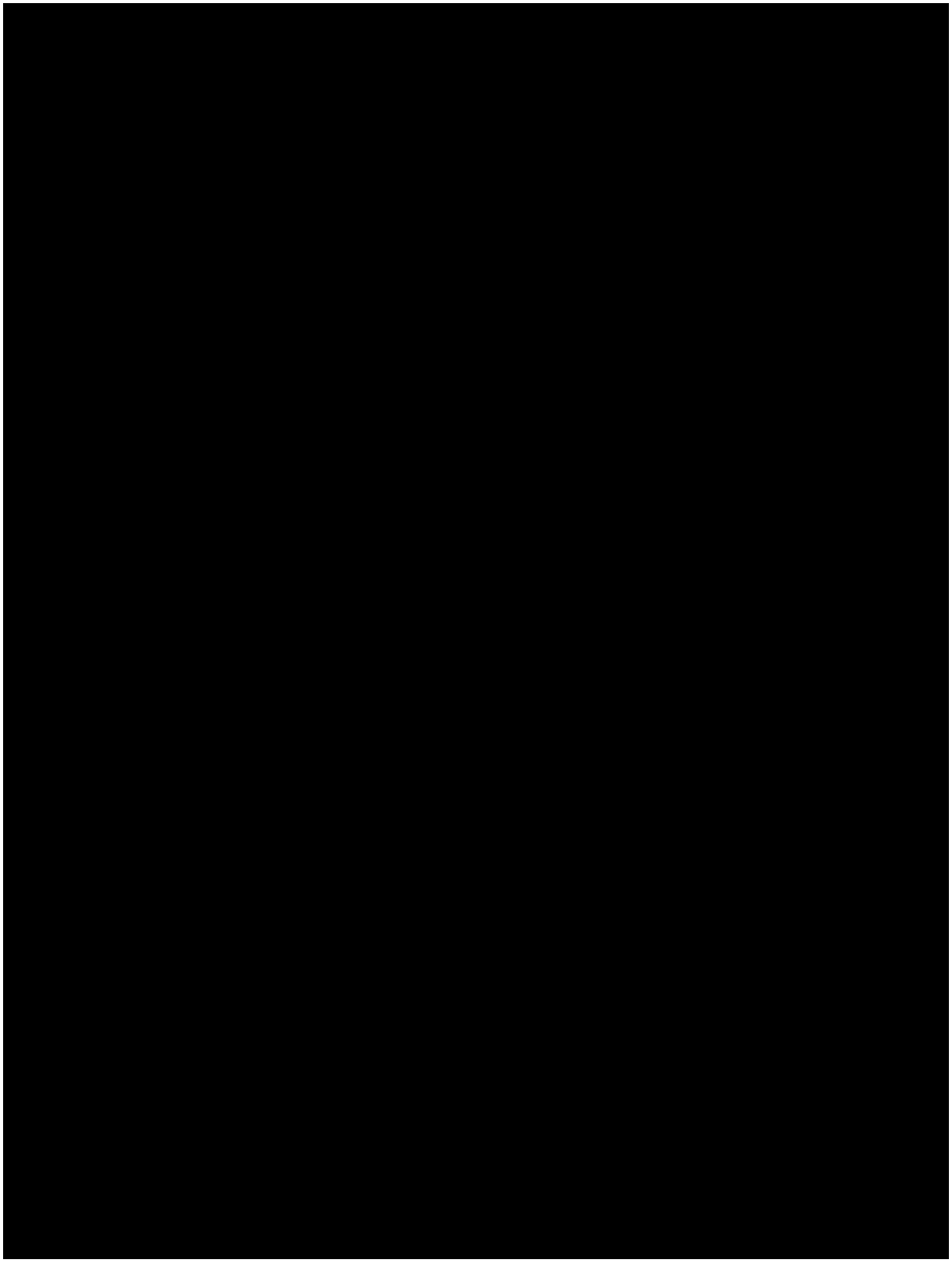
In the case of data not being normally distributed, nonparametric tests, such as Wilcoxon Rank Sum test, will be utilized to assess the treatment efficacy.

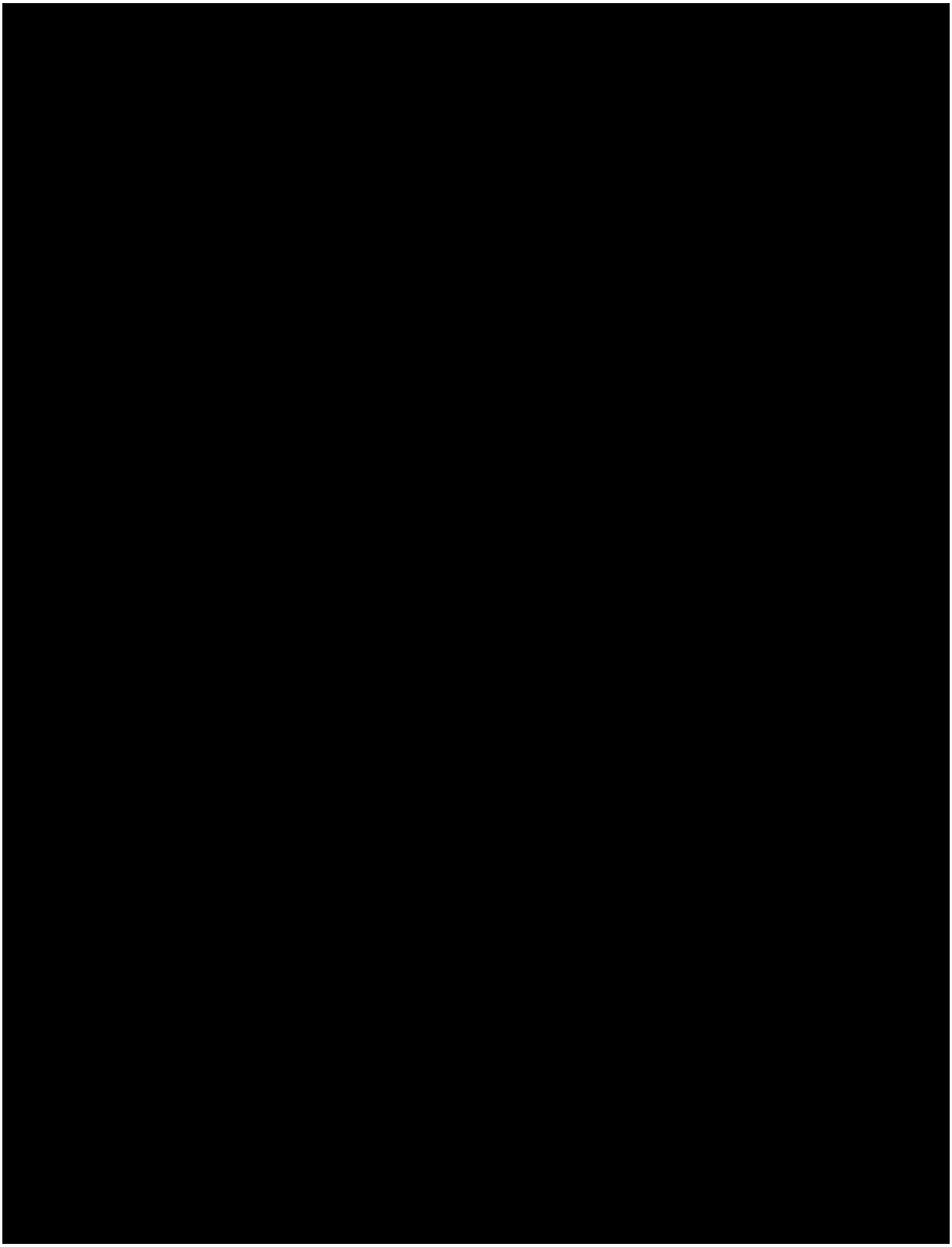
7.1.5 Exploratory Analyses

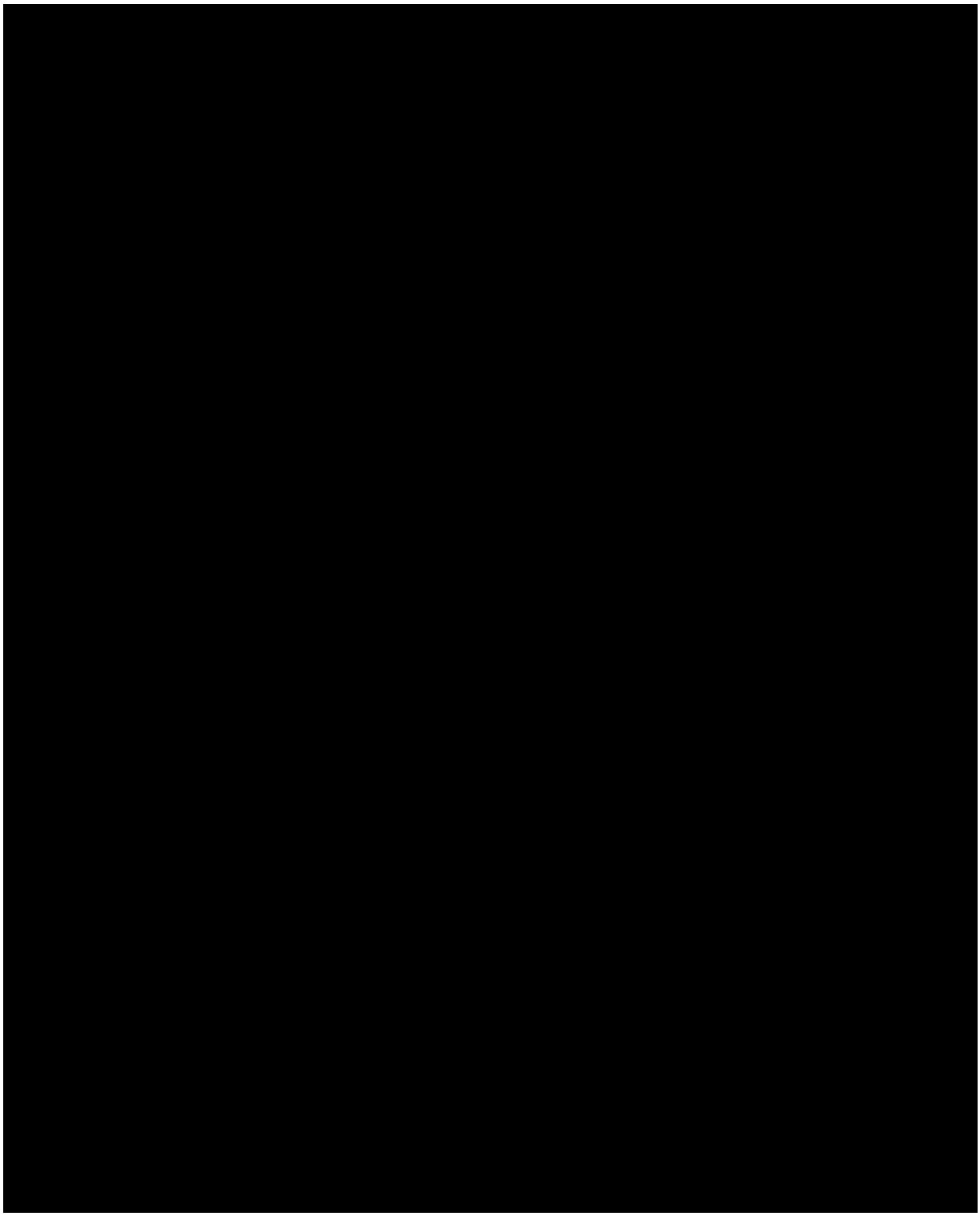
[redacted]











7.1.6 Adjustments for Covariates

Not applicable.

7.1.7 Disposition of Subjects

The number and percentage of subjects enrolled, randomized, treated, early termination in the study will be presented. Reasons for any screen failures and/or early terminations, including the relationship to COVID-19 related study disruption, will be summarized. In addition, the number and percentage of subjects who deviated from the study, including the relationship to COVID-19 related study disruption, will also be summarized.

7.1.8 Description of Demographics and Baseline Characteristics

Demographic data, baseline characteristics, medical history, and concomitant medications will be summarized by means of descriptive statistics (number, mean, SD, median, minimum, and maximum) or frequency tables and analyzed using t-tests, chi-square tests, or Fisher's exact tests, as applicable. A listing of subjects affected by the COVID-19 related study disruption will be presented.

7.1.9 Study Site Assessment

In addition to adjusting for study site in the primary efficacy analysis, in order to evaluate the consistency of efficacy across sites, subgroup analysis by study site will also be conducted. Study sites with less than 10 subjects will be analyzed using pooling techniques to provide more reliable inferences across sites.

7.1.10 Subgroup Analyses

Exploratory analysis on efficacy parameters will be conducted on gender, age, BMI, and smoking status.

7.1.11 Planned Interim Analyses

7.1.12 Multiple Comparisons / Multiplicity

There will be one interim analysis conducted when the study population reaches 50% of the total expected and a second interim analysis conducted after all subjects have completed the 180-day visit. Type I error will be adjusted for the interim analyses as mentioned in Section 7.1.11. Furthermore, one final analysis will be conducted upon study completion, which should mitigate any concerns of multiplicity.

7.1.13 Handling of Dropouts or Missing Data

Missing data is expected to be minimal; however, there is a chance that some subjects will not have full, complete data for the entire analysis. Missing data for efficacy assessments will be imputed using the Last Observation Carried Forward (LOCF) approach. In conjunction, Observed Case data, reported data without imputation, will also be analyzed to assess the sensitivity of the analysis to the choice of imputation approach.

7.2 Safety Evaluation

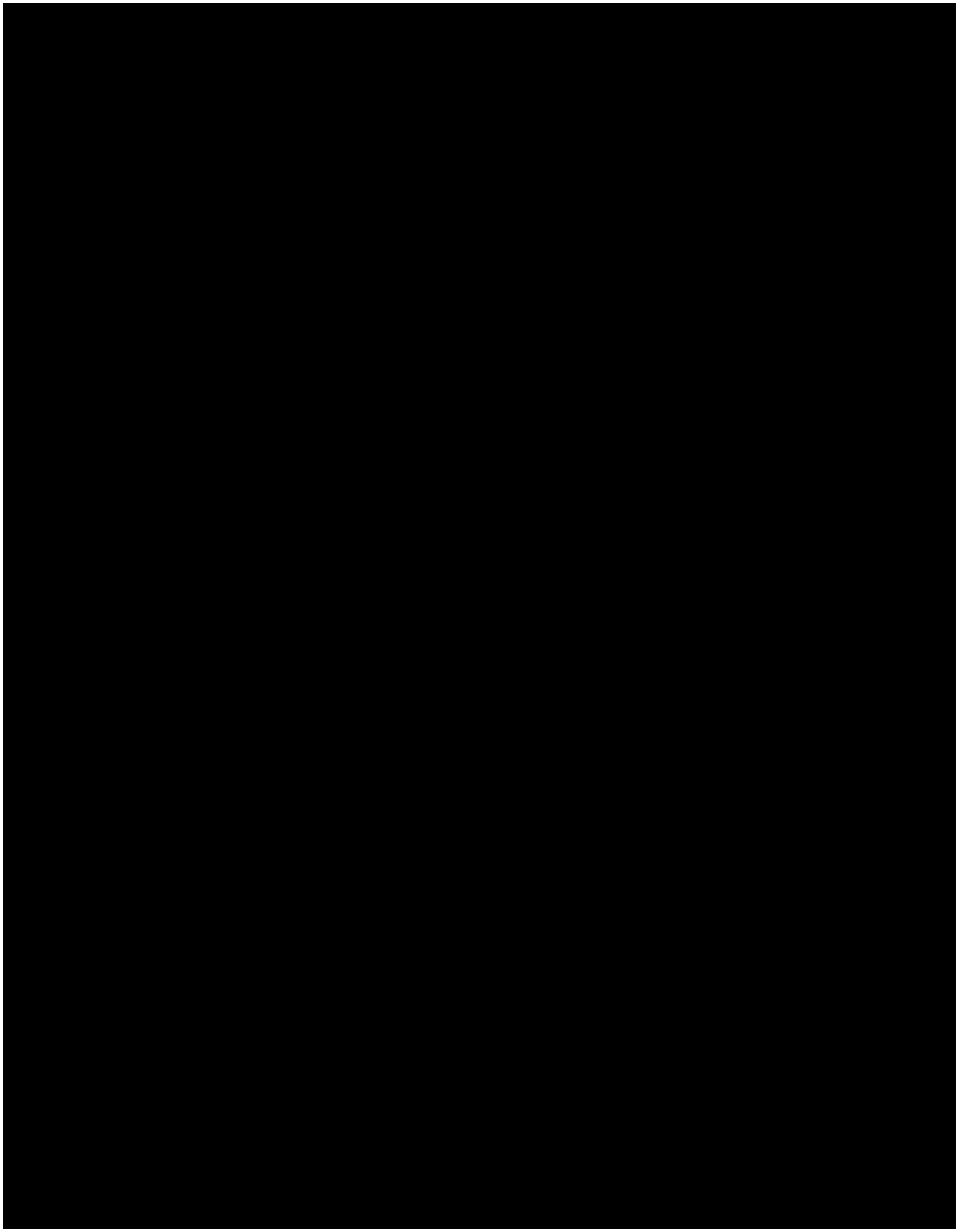
The safety endpoint of this study is the proportion of product-related AEs, SAEs, and unanticipated adverse events throughout the study in the micronized dHACM versus placebo-treated group. All enrolled subjects who receive at least one injection will be

used for the analysis of safety data. A listing of AE affected by the COVID-19 related study disruption will be presented.

The incidence of all treatment emergent adverse events and serious adverse events as well as major complications (product related) will be compared between the two treatment groups. Safety will also be reported as the frequencies of occurrence of each adverse event, the rate of adverse events per subjects/year and time to each event. In addition, the number of subjects with each serious adverse event type will be reported.

7.3 Changes in the Planned Statistical Methodology

7.4 Presentation of Statistical Tables, Figures, and Data Listings



[redacted]

7.5 Electronic Datasets

[redacted]

8 APPENDICES

None.

9 REFERENCES

[redacted]

10 RELATED DOCUMENTS

11 REVISION HISTORY