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Treatment Groups	Cohort 1: Investigational Medicinal Product -hMaxi-K (8000 or 16000 µg) Cohort 2: Placebo (PBS sucrose 20%)
Protocol Number	ION04ED
Protocol Title	A Double-blind, Placebo-controlled, Parallel Design, Randomized Phase 2A Trial Evaluating the Potential Activity and Safety of *h*Maxi-K Gene Transfer in Males with Erectile Dysfunction.
Sponsor	Ion Channel Innovations, LLC
Contract Research Organization	[redacted]

Revision Chronology		
Version	**Effective Date**	**Reason for change**
0.1	15th December,2014	Initial Version
0.2	18th December, 2014	Updated with input from CRF
1.0	29th January, 2015	Updated based on client comments
2.0	18th July, 2017	Updated based on client comments
3.0	04th August, 2017	Included list of outputs
4.0	16th November, 2017	Updated list of outputs
5.0	12th December, 2017	Updated primary analysis section and list of outputs
6.0	14th December, 2017	Incorporated clarifications from client/sponsor

Approved By	
Signature	
Date	

1. Table of Contents

2. List of Abbreviations

Term	Definition
AE	Adverse event
DLT	Dose Limiting Toxicities
ED	Erectile Dysfunction
EF	Erectile Function
ECG	Electrocardiogram
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CRF	Case Report Form
IIEF	International Index of Erectile Function
IU	International Unit
IC	Intracavernous
ITT	Intent-to-treat
Mod-ITT	Modified Intent-to-treat
PP	Per protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin
SEP	Sexual Encounter Profile
SEP2	Ability to achieve vaginal penetration
SEP3	Ability to maintain an erection long enough for successful intercourse
Sed. rate	sedimentation rate
VED	Vacuum Erection Devices

3. Introduction

Erectile Dysfunction (ED) is a disease defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual function. The most common cause of ED is advanced age. Proposed causes of age-induced ED include reduction of NO production, increased contractility of the smooth muscle of the penile corpora, increased myofilament calcium sensitivity due to altered *Rho* kinase expression/activity, and reduction in the relative percentage of smooth muscle fibers and an increase in collagen content thus decreasing the compliance of the cavernous tissue. The second most common cause is diminished blood flow to the penis due to cardiovascular disease.

ED can either be reversible or nonreversible. Men over 50 years tend to have permanent causes of ED that are disease-related. The most frequently associated diseases include atherosclerosis, hypertension, anti-hypertensive medications, diabetes mellitus, and pelvic surgery and radiation. In younger men (ages 20 – 40), psychological causes for ED often predominate and this reversible form of ED can be treated with sex therapy and drugs.

Ion Channel Innovations has developed *h*Maxi-K to treat ED using the same principal as drugs that have been used since 1982, i.e., treatment with medicines causing relaxation of the penile smooth muscle resulting in rigid erections. *h*Maxi-K consists of the gene for the α-pore subunit of the maxi-K channel, *hSlo*, inserted into a plasmid vector. Administration of this gene into the corpora increases expression of the maxi-K channel in the smooth muscle cells and an increased efflux of K+ across the cell membrane resulting in decreased entry of Ca++ ions. This effect on ion exchange across the smooth muscle cells allows the smooth muscle of the corpora to relax; the corporal sinusoids become engorged with blood, and the penis to stay rigid. Furthermore, results from these preclinical studies suggest that expression of the α-pore subunit for the maxi-K channel following administration of *h*Maxi-K may have a long-term effect on the erectile mechanism. This activity of *h*Maxi-K may represent a distinct advantage over current drug therapy for ED where the effect of treatment is temporary.

This statistical analysis plan describes in detail the methods and presentation of the data analyses for the study ION04-ED to evaluate the safety and efficacy of a single intracavernous injection of *h*Maxi K (8000 µg and 16000 µg) or placebo upon penile rigidity or erection in males with erectile dysfunction longer than six months that is attributable to an underlying, stable medical condition.

This study is double-blind, placebo controlled parallel design Phase 2A trial evaluating the potential activity and safety of two different doses of *h*Maxi-K (16000 µg, and 8000µg) given in a single administration relative to placebo injected into the corpus cavernosum of the penis. The proposed study period is approximately 6 months following the single injection of study drug per participant. This study will enroll 11 participants at *h*Maxi-K doses of 8000 µg, 11 participants at *h*Maxi-K doses of 16000 µg and 13 on placebo. A maximum of 35 participants will be enrolled.

Schedule of Events

Test or Procedure	Visit 1 -2 Week Screening	Visit 2 Week 0	Visit 3 Week 1 ± 2 days	Visit 4 Week 4 ± 3 days	Visit 5 Week 8 ± 3 days	Visit 6 Week 12 ± 3 days	Visit 7 Week 24 ± 3 days
Informed Consent Process	X						
Medical History	X	X[5]	X	X	X	X	X
Physical Examination	X	X[5]	X	X	X	X	X
Physical Examination of Penis[1]	X	X[5]	X	X	X	X	X
Blood Tests (Chemistry and Hematology)[2]	X[4]		X	X		X	X
Urine analysis[3]	X	X[5]	X	X		X	X
ECG[4]	X	X[4]	X	X	X	X	X
IIEF[5]	X	X[5]	X	X	X	X	X
SEP[5]		X[5]	X	X	X	X	X
Study drug administration		X					
Assay for *h*Slo DNA[6]	X[6]	X	X	X	X	X	X

[1]PE of penis includes: inspection, palpation and neurosensory testing

[2]Blood tests include: Hematology (CBC with differential, platelet count, PTT, PT, sedimentation rate, CRP), Chemistry (BUN, Cr, Na^+, K^+, Mg^{++}, Ca^{++}, CO_2, Cl, albumin, alkaline phosphatase, ALT, AST, total bilirubin, total protein; Endocrine (testosterone, random cortisol, TSH, T4). Hemoglobin A1c and prolactin at Screening (V1) only.

[3]Urine analysis includes: microscopic RBC and WBC, protein, glucose, and specific gravity.

[4]ECG at V2 will be done prior to administration of study drug and at 1 and 2 hours following administration of study drug

[5]Test will be done prior to administration of study drug.

[6]In all participants, plasma specimens will be collected to assay for the presence of *h*Slo DNA by PCR. At Visit 2 collect pre- dosing and 2 post dosing.

4. Study Objective

The objective of the study is to evaluate the safety and efficacy of a single intracavernous injection of *h*Maxi K (8000 µg and 16000 µg) or placebo upon penile rigidity or erection in males with erectile dysfunction longer than six months that is attributable to an underlying, stable medical condition.

Primary objective

The primary objective of this study is to evaluate the potential efficacy and safety of a single intracavernous injection of *h*Maxi-K (16,000 µg) compared to placebo in males with erectile dysfunction longer than six months that was attributable to an underlying, stable medical condition upon penile rigidity or erection in males with erectile dysfunction longer than six months that is attributable to underlying, stable medical condition.

Secondary objective

The secondary objective of this study is to evaluate safety of a single intracavernous injection of *h*Maxi-K, either 8,000 or 16,000 µg, compared to placebo.

Study Endpoints

The primary outcome measures that will be considered to evaluate change in erectile status from baseline following administration of *h*Maxi-K are

- Erectile Function (EF) domain of the International Index of Erectile Function (IIEF)

- Sexual Encounter Profile (SEP)-Questions 2 and 3

The safety and tolerability of the study drug will be evaluated by analysis of

- Adverse events
- Clinical laboratory tests
- Electrocardiogram
- Physical examinations including vital signs

5. Analysis Sets

- **Randomized population**: This will include all the subjects who have been randomized to either of the treatment groups.
- **ITT population**: This will include all the subjects who have been randomized to either of the treatment groups and who have received at least one dose of study treatment.
- **Modified ITT population (Mod-ITT population)**: This population will include all subjects in the ITT population who have at least one post dose efficacy assessment.
- **Per Protocol Population (PP Population):** This will include all subjects in the ITT population who report no protocol violations.
- **Safety Population**: This will include all subjects who were randomized to either of the treatment groups and who have received at least one dose of study treatment.

6. Definition

- **Age:** The age will be calculated as the exact number of days between the date of birth and date of informed consent converted to years (i.e. difference in days/365.25). Age is the integer part of this value.
- **Baseline:** The time point at which randomization is performed will be the baseline time point. The last instance of data collected before administration of treatment will be considered as the baseline information for the respective parameter. If a patient has repeated assessments prior to the start of double-blind study drug, then the results from the final assessment made prior to the start of double-blind study drug will be used as baseline.
- **Body Mass Index (BMI):** BMI is obtained by dividing the weight (kg) by the square of height (m) i.e. weight (kg)/ height^2 (m).
- **Change between baseline and post dose visits** for the parameters will be considered as the difference between the post baseline value and the baseline value (post baseline value – baseline value). This will be applicable to laboratory data and safety parameters.
- **Prior/ Concomitant Medication/Therapy:** All medications/therapies with end date prior to the date of treatment will be considered as prior medications. Concomitant medication will be defined as any medication taken between the day of dosing with study drug and the end of the 6 month study follow-up period (or final visit). Any medications started after the final visit will not be considered concomitant medications.
- **Treatment Emergent Adverse Events (TEAEs):** A treatment emergent adverse event (TEAE) will be considered as an event that is temporally associated with the use of the study drug, whether or not considered related to the study drug. All adverse events with start date on or after the date of treatment will be considered as TEAEs.

- **Serious Adverse Events:** Serious adverse events are defined as the adverse events which are medically significant events (e.g., intensive treatment in ER or at home for allergic bronchospasm), life threatening, requiring hospitalization or resulting in death, a disability, or a congenital abnormality.

7. Data Handling

Analysis using Last Observation Carried Forward (LOCF) will be used for handling missing data. Further, with regard to missing data, the assumption of missing at random will be assessed by looking for patterns over time, and by comparing those with missing values to all other subjects with regard to baseline characteristics. Chi-square or Exact tests will be used to compare incidence rates among the treatment cohorts with respect to the below baseline characteristics

- Demographics (date of birth, age, race, weight, height, and body mass index [BMI])
- Assessment of physical examination
- Abnormalities in ECG parameters
- Abnormalities in vital sign parameters
- Efficacy endpoints
- Safety endpoints
- Prior and concomitant medication

8. Sample Size Calculations

The study population includes men with erectile dysfunction attributable to an underlying, stable medical condition but who are otherwise in good health. The most common stable medical diseases that cause erectile dysfunction include hypertension and atherosclerosis, antihypertensive medication, type I and type II diabetes mellitus, pelvic surgery and pelvic radiation, cerebrovascular accidents (stroke), multiple sclerosis, and Parkinson's disease. Men with erectile dysfunction secondary to aging as a solitary cause will not be included in the trial. Serum Prolactin levels will have been obtained on the participants as part of their work up for erectile dysfunction. The target population is men with erectile dysfunction who have been unable to tolerate, do not wish to continue, or have had unsuccessful results with, prior therapy for ED.

The sample size has been estimated assuming a standard deviation of 2.5 and a two sample t-test to have 80% power.

Statistical Power									
Power	**N1**	**N2**	**Placebo**	**Ratio**	**Alpha`**	**Mean1**	**Mean2**	**SD1**	**SD2**
80%	11	11	13	1.111	0.0167	10.0	6.6	2.5	2.5

Alpha' is the alpha level adjusted for three multiple comparisons (the two doses compared with each other, each dose compared with the placebo, and total active treatment (two doses combined) compared to placebo. Given the three comparisons that incorporated a Bonferroni multiple comparison procedure, the overall alpha level is preserved at .05.

A 10% attrition rate over the 24 weeks of follow-up is anticipated, which inflates the sample size to approximately 40 subjects in total.

9. Statistical Methods

This section describes the various statistical analyses that are planned to be performed for this study. The primary analysis which includes efficacy analysis will be performed on the mod-ITT population and supportive analysis on the PP and ITT populations. The safety endpoints will be evaluated on the safety population.

If a patient has repeated assessments prior to the start of double-blind study drug, then the results from the final assessment made prior to the start of double-blind study drug will be used as baseline. If end-of-study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all post-baseline assessments will be presented in the data listings.

Dose response comparisons will be made between 8000 mcg vs. 16000 mcg vs. placebo as well as comparisons between total active population (8000 mcg and 16000) vs. placebo. Onset and duration of effect will also be analyzed and a dose response evaluated. Onset and duration of action will also be analyzed.

All tests of significance with regard to efficacy will be one-tailed, and performed at an overall alpha level of .05. All estimates of differences will be presented with 95% confidence limits.

9.1. Analysis Conventions

The following conventions will be applied to all data presentations and analyses.

- ❑ Tables and listings will be presented in landscape orientation.
- ❑ Tables will be presented for analysis populations as defined in the title of the tables.
- ❑ Listings will be presented for the enrolled population.
- ❑ All the displays will be in Tahoma 8pt font.
- ❑ All tables and listings will have footer sections which will contain the name of the program.
- ❑ For all tables and listings, the titles will appear in the body of the document. The title will include the sponsor name, protocol name, date and time of generation, version (Draft/Final), page number in the format Page X of Y, Table/Listing number and name.

An example is given below

Ion Channel Innovations, LLC		Draft –DDMMMYYYY:HH:MM
Protocol: ION04ED		Page x of y
Table XX.X.X		
Table Title		
Population		

- ❑ Summary tables will contain footnotes in the body of the title that reference any data listings or tables associated with the table or figure (e.g. Reference: Listing 16.X.XX).
- ❑ Additional footnotes may be added as per the STL shells.
- ❑ The outputs have to be created as per the shells that will be provided along with this analysis plan.
- ❑ Guidelines provided in the STL shells under "Programming notes" should be referred to by the programmers for clarity on shells.
- ❑ All means and medians will be formatted to one more decimal place than the measured value. Confidence intervals and standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- ❑ The number and percentage of responses will be presented in the form XX (XX %) where the percentage as whole numbers will be in parentheses.

- ❑ All p-values will be presented with at least 3 decimal places ensuring meaningful representation.
- ❑ All summary tables will include the total number of subjects in the population that is being analyzed based on treatment randomized and received study drug. This information will be given in the column headings in each table.
- ❑ All listings will be ordered by treatment cohort, subject number and visit date (if applicable).
- ❑ Date variables will be formatted as DDMMMYYYY for presentation.
- ❑ SAS® Version 9.2 will be used for all data analysis.
- ❑ MedDRA version 19.1 and WHO version released on DEC 01, 2017 will be used for coding adverse events and concomitant medications, respectively.

9.2. Descriptive Methods

The study comprises of two cohorts comprising of three treatment groups namely

- **Cohort 1:** *h*Maxi-K- comprising of two treatment groups; *h*Maxi-K 8000µg and *h*Maxi-K 16000µg
- **Cohort 2:** Placebo- which was administration of PBS-20% sucrose

All outputs will be presented with respect to the above two cohorts and overall. Cohort 1 will be further sub-categorized with respect to the two treatments.

The various baseline and demographic characteristics will be analyzed for the randomized population. For quantitative variables, the following descriptive statistics will be computed: number of subjects (n), number of missing values/subjects, mean, standard deviation, minimum, maximum, median, Q1 and Q3. For qualitative variables, the frequency and percentage of subjects and/or events will be calculated. All listings will include the subject identifiers, the treatment group/cohort that the subject is randomized to and the tables will be presented by the treatment cohorts to which subjects are randomized. The characteristics that will be analyzed are as follows

❑ Demography

At screening, demographic data including: date of birth, age, race, height and weight. The date of birth, age, height, weight and BMI will be listed in the demography listing. In addition to this, the information pertaining to subject being diabetic, informed consent and the analysis population flag will be presented.

In addition, descriptive statistics for relevant variables will be presented in tabular format. The age and BMI will be calculated as mentioned in section 6 of this document. Age, height, weight and BMI will be summarized by number of subjects (n), number of missing values/subjects, mean, standard deviation, minimum, maximum, median, Q1 and Q3. Categorical parameters namely race and subject being diabetic will be summarized using counts and percentages. The percentages will be calculated based on the number of non-missing values.

❑ Medical History

Medical History terms will be coded using MedDRA version 19.1. A listing will be created to present the medical history information collected in the CRF. A table will be created to present the count and percentage of subjects with medical conditions falling under each body system and preferred term within each body system.

❑ Physical examination

A complete review of body systems will be performed at all visits as part of physical examination. The number and percentage of subjects having normal, abnormal or not done responses against each body system at screening and post-dose visits 1-7 (week -2 - 24) will be tabulated. The corresponding listing will present the body system, responses and details of abnormalities (if applicable).

❑ Physical Examination of Penis

Physical examination of the penis will be done at all visits and will include inspection, palpation and neurosensory testing. The percentage of subjects having normal, abnormal or not done responses against each parameter will be tabulated. The corresponding listing will present the parameter, responses and details of abnormalities (if applicable).

❑ Electrocardiograms

A 12-lead ECG will be performed at screening and post-dose visits 1-7 (week -2 - 24). The descriptive statistics for the following parameters will be presented: heart rate, PR interval, QT interval, QTc, QRS duration, QRS axis, QTcF, QTcB and RR duration. The number and percentage of subjects under each categorization of rhythm and overall evaluation will be further presented. The corresponding listing will include the results against above parameters, significance, details of clinically significant results and differences from previous assessment. Both the ECG overreader's reading and site readings will be evaluated. Shift tables will also be presented for the relevant parameters.

❑ Vital Signs

Vital signs will be collected at all visits. Vital signs will include

- Brachial blood pressure (BP)
- Pulse rate
- Oral temperature
- Weight

Descriptive statistics will be presented for all the above parameters at all the time points of collection with respect to the treatment cohorts. The corresponding listing will present the results.

❑ Prior and Concomitant Medication

Prior and concomitant medications will be listed and tabulated. Listings will present the information collected against these terms and a flag to identify prior and concomitant medications. Separate tables will be generated to present the counts and percentages of subjects with prior and concomitant medications falling in each therapeutic class and chemical subgroup (obtained as part of WHODD coding).

❑ Inclusion/Exclusion criteria

The information pertaining to the inclusion and exclusion criteria will be listed.

❑ Compliance to study medication

The subjects are planned to be assigned to one of the below treatment cohorts

- **Cohort 1:** *h*Maxi-K- comprising of two treatment groups; *h*Maxi-K 8000µg and *h*Maxi-K 16000µg
- **Cohort 2:** Placebo- which was administration of PBS-20% sucrose

Compliance to study medication will be summarized and listed. The summary table will include the number and percentage of subjects randomized to the two treatment cohorts. Further categorization on the treatments administered within each cohort will be provided. It will also include the number and percentage of subjects who were administered treatment. The listing will include the details pertaining to treatment cohort, treatment, randomization number, date of administration and whether treatment was administered.

❑ Randomization

The data pertaining to the treatment to which subject has been randomization will be listed.

❑ Protocol Deviations

List of protocol deviations will be provided by the CRO and this will be classified into minor or major based on inputs from the sponsor. The subjects reporting protocol deviations will be listed along with the deviation and its classification.

❑ Study Termination

The study completion listing will be developed based on the data obtained in the study termination form. The listing will include the date of completion/withdrawal, status at the end of study, main reason for not completing, date of last contact and date of death (if applicable). All patients who prematurely discontinued during the study will be listed by discontinuation reason for the randomized ITT Population.

❑ Subject Disposition

A table representing the counts and percentages of subjects attaining the various study milestones namely enrolment, randomization, meeting analysis population criteria, protocol deviations and study completion or withdrawal will be presented. The reason for discontinuation will also be summarized within the table.

❑ Efficacy endpoints

The International Index of Erectile Function (IIEF) is a validated, self-administered questionnaire that has been shown to be a cross-culturally and psychometrically valid measure of male erectile dysfunction.

The test contains 15 questions in five domains:

a) erectile duration/function (six items)
b) orgasmic function (two items)
c) sexual desire (two items)
d) intercourse satisfaction (three items)
e) overall sexual satisfaction (two items)

The summary tables against the data collected through the IIEF will include the descriptive statistics against the total and domain specific score by visit. The domain specific scores will be the sum of the scores against questions under the respective domain. The total score will be the sum of scores of all the questions. The listings will also be presented against all the data that is collected.

SEP is a diary in which subjects record each sexual attempt made throughout the study and is composed of 5 questions assessing sexual function. SEP 2 evaluates the penetrability of the erection and SEP 3 the maintenance of the erection.

The summary tables against SEP will include the number and percentages of subjects reporting yes/no against each of the questions. Corresponding listing will also be presented.

In addition to the summary tables, tables will be presented against the analysis mentioned in the below section.

9.3. Primary Analysis

The primary outcome measures that will be considered to evaluate change in erectile status from baseline following administration of *h*Maxi-K are

- ❑ Erectile Function (EF) domain of the International Index of Erectile Function (IIEF)
- ❑ Sexual Encounter Profile (SEP): Questions 2 and 3

❑ **Erectile Function (EF) domain of the International Index of Erectile Function (IIEF)**

The erectile function domain, questions 1-5, and 15 of the IIEF has been validated to assess erectile changes only. The IIEF EF domain has a 30-point total score, where higher scores reflect better erectile function. The EF domain of the IIEF will be completed at Visit 1 (screening) and V2-V7 (week 0-24).

The total score for a subject for the EF domain will be computed as the sum of the six questions. Descriptive statistics of the domain score will be presented with respect to the subjects receiving *h*Maxi-K (16,000 µg) and placebo at all visits. The change in scores from baseline at each visit will be evaluated using one-sided paired t-test at 5% significance level to assess improvement in scores post treatment when compared to baseline for the two treatment groups separately. Further, a one-sided two sample t-test will be applied to compare the changes from baseline in scores between the two treatment groups. The scores for the other 4 domains on the IIEF will also be computed and analyzed as secondary analyses.

Repeated measures ANOVA will be performed to assess the effect of visit on the total score for each treatment groups. Further a two-sample t test, will be performed to study the effect of treatment groups and time points on the domain scores.

The above analysis will be repeated for comparison between the two treatment cohorts and between *h*Maxi-K 8000µg and placebo treatment groups.

Analysis will be performed including all subjects and the final 15 subjects separately.

❑ **Sexual Encounter Profile (SEP): Questions 2 and 3**

The two questions from the Sexual Encounter Profile (SEP) deal with the ability to achieve vaginal penetration (SEP2), and the ability to maintain an erection long enough for successful intercourse (SEP3) will be analyzed as part of this study. This questionnaire will be completed at V2-V7 (week 0-24).

Chi-square analysis will be performed to compare the responses at each post dose visit with baseline response for the two treatment groups, namely, hMaxi-K (16,000 µg) and placebo. In addition, repeated measures logistic regression will be performed to analyze the effect of treatment groups and time points on the response to the SEP questions. The baseline and post baseline score for each SEP question will be a patient's percentage of "yes" responses to that question during the baseline and post baseline period, respectively.

ANCOVA will be used to analyze the mean change in SEP response from baseline to post baseline visits between hMaxi-K (16,000 µg) and placebo.

The above analysis will be repeated for comparison between the two treatment cohorts and between *h*Maxi-K 8000µg and placebo treatment groups.

9.4. Safety and/or further analysis

The below parameters will be analyzed against the safety population as part of the safety analysis

- ❑ Adverse events
- ❑ Serious Adverse Events
- ❑ Clinical laboratory tests
- ❑ Electrocardiogram
- ❑ Physical examinations and Vital signs
- ❑ Pharmacokinetics Evaluations (Assays for *h*slo Maxi-K)

❑ **Adverse Events**

All the adverse events will be coded using the MedDRA Version 19.1. All the information collected in the AE form in the CRF and the preferred term, and system organ class corresponding to each reported term will be presented as a listing. In addition to this SAEs will be presented as a separate listing.

An overall summary table for the adverse events will be presented. All TEAEs recorded during the study will be further summarized in detail. The incidence of adverse events will be summarized by system organ class and preferred term within system organ class overall and by severity, relationship, outcome, action taken separately and DLT.

Summary tables corresponding to the AEs will contain the incidence of events and the number and percentage of subjects experiencing an adverse event. The percentages will be calculated with respect to the total number of subjects in the safety population. While counting the number of subjects, a subject with more than one adverse event with the same preferred term will be counted only once using the incidence with highest severity (severity, action taken and DLT tables), or strongest relationship to study treatment and most severe outcome for the respective tables. The descending order of the above characteristics will be considered as below

- **Severity /Toxicity grade**
  - Severe
  - Moderate
  - Mild
- **Relationship**
  - Definitely Related
  - Probable
  - Possible
  - Unrelated
- **Outcome**
  - Condition Deteriorated
  - Still Present
  - Improving
  - Recovered with Sequela
  - Recovered
  - Other

Serious AE are defined as the following:

- Medically significant events (e.g., intensive treatment in ER or at home for allergic bronchospasm)

- life threatening
- requiring hospitalization
- resulting in death
- resulting in a disability
- resulting in a congenital abnormality

Similar tables will be presented for serious adverse events. Deaths will be reported as AE term in the CRF. Deaths and other serious adverse events will be listed.

❑ **Clinical laboratory tests**

The following laboratory tests will be performed at different visits as indicated in the flow chart in section 3 above

- Hematology including complete blood count (CBC) with differential
- Chemistry
- Urine Analysis
- Endocrine Tests

All results corresponding to laboratory evaluations will be presented in IU units. The laboratory results will be listed by treatment cohorts, subject and visit. Abnormal results will be flagged as H or L based on values being above or below the normal range respectively. Values within the normal ranges will be flagged as N.

The frequency of number of incidences of laboratory abnormalities will be displayed by parameter and treatment cohort with respect to the classification of values based on the normal range. Descriptive statistics will be presented for laboratory results with respect to treatment cohort and visit. Further, the change from baseline at each post dose visit will be presented descriptively in accordance to the plan of data collection. Descriptive statistics for the change from baseline to the last available on treatment visit will also be presented. Shift tables will be presented for each analyte to assess the change in abnormalities over visits.

❑ **Electrocardiogram**

As part of the analysis for this safety endpoint, in addition to the analysis suggested in section 9.2 above, changes from baseline at each post dose visit will be presented. Number and percentage of subjects reporting abnormalities will further be tabulated with respect to treatment cohort and visits for both the over reader and site evaluations. Shift tables will also be presented to study the change in abnormalities over the visits.

❑ **Physical examinations and vital signs**

In addition to the analysis mentioned in section 9.2, the descriptive statistics for change from baseline at post dose visits will be presented for the below parameters

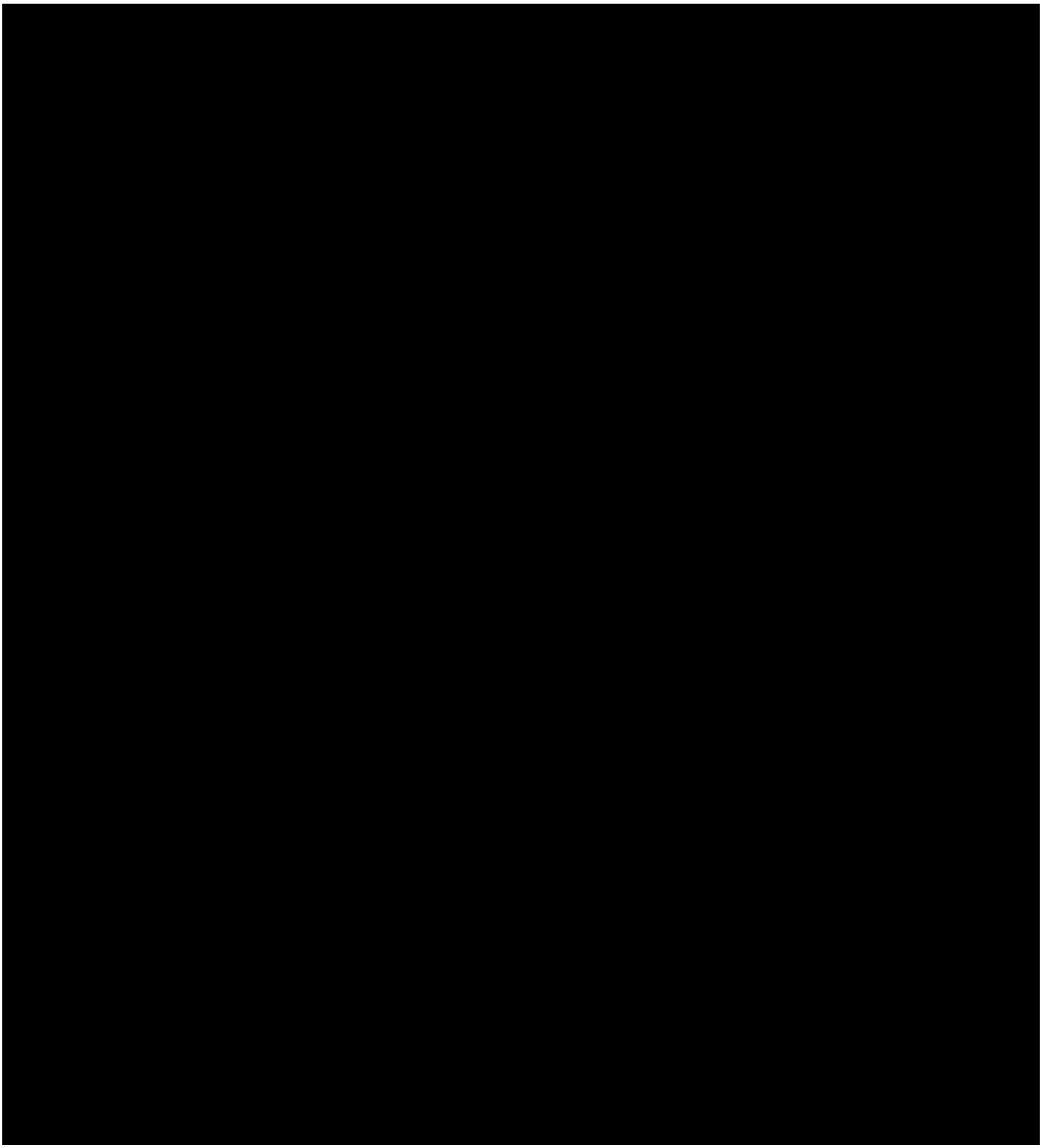
- Heart rate
- Blood pressure
- Weight
- Oral Temperature

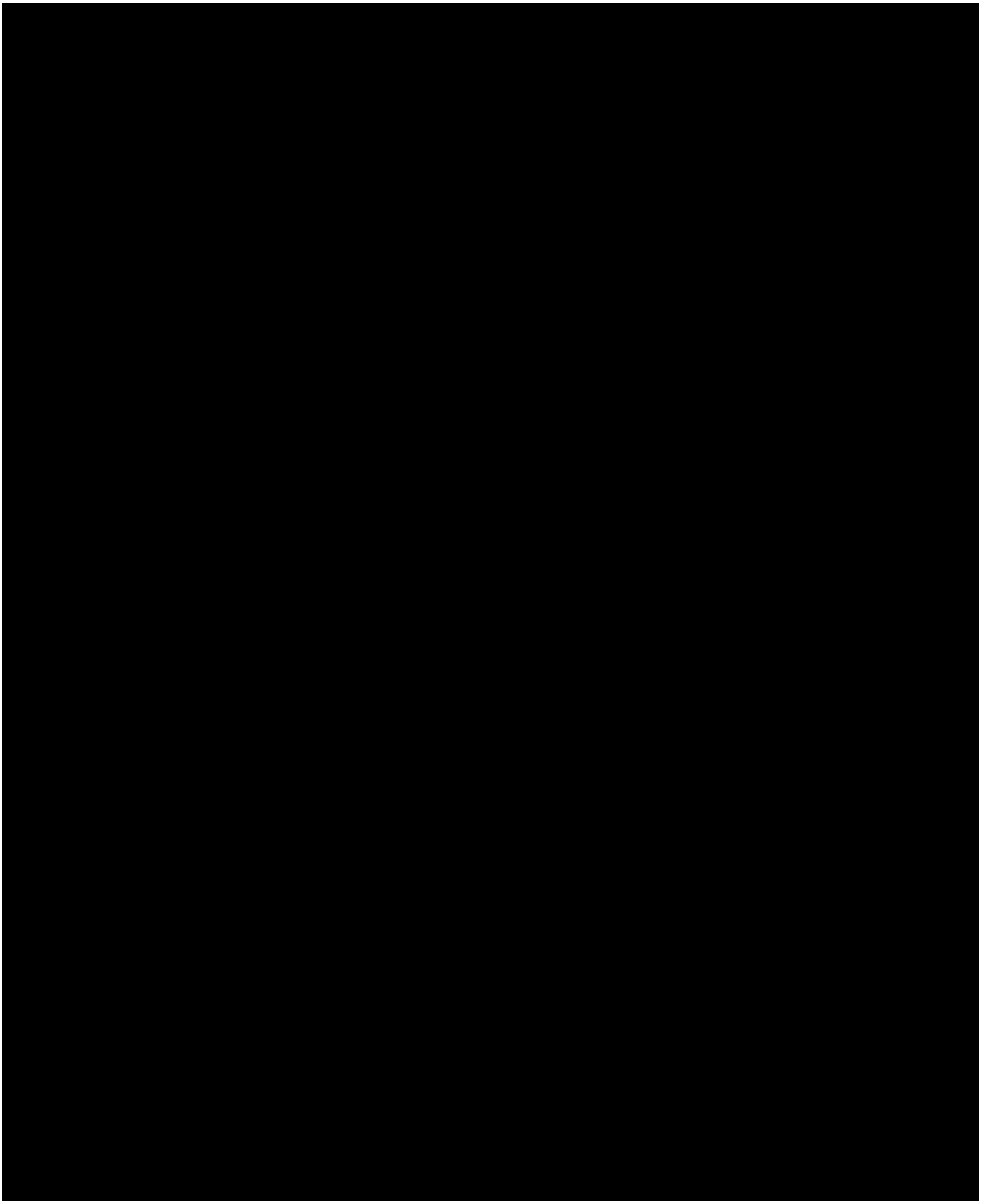
Further, the number and percentage of subjects reporting abnormalities for above parameters and during physical examination of the penis will be tabulated with respect to treatment cohort and visits.

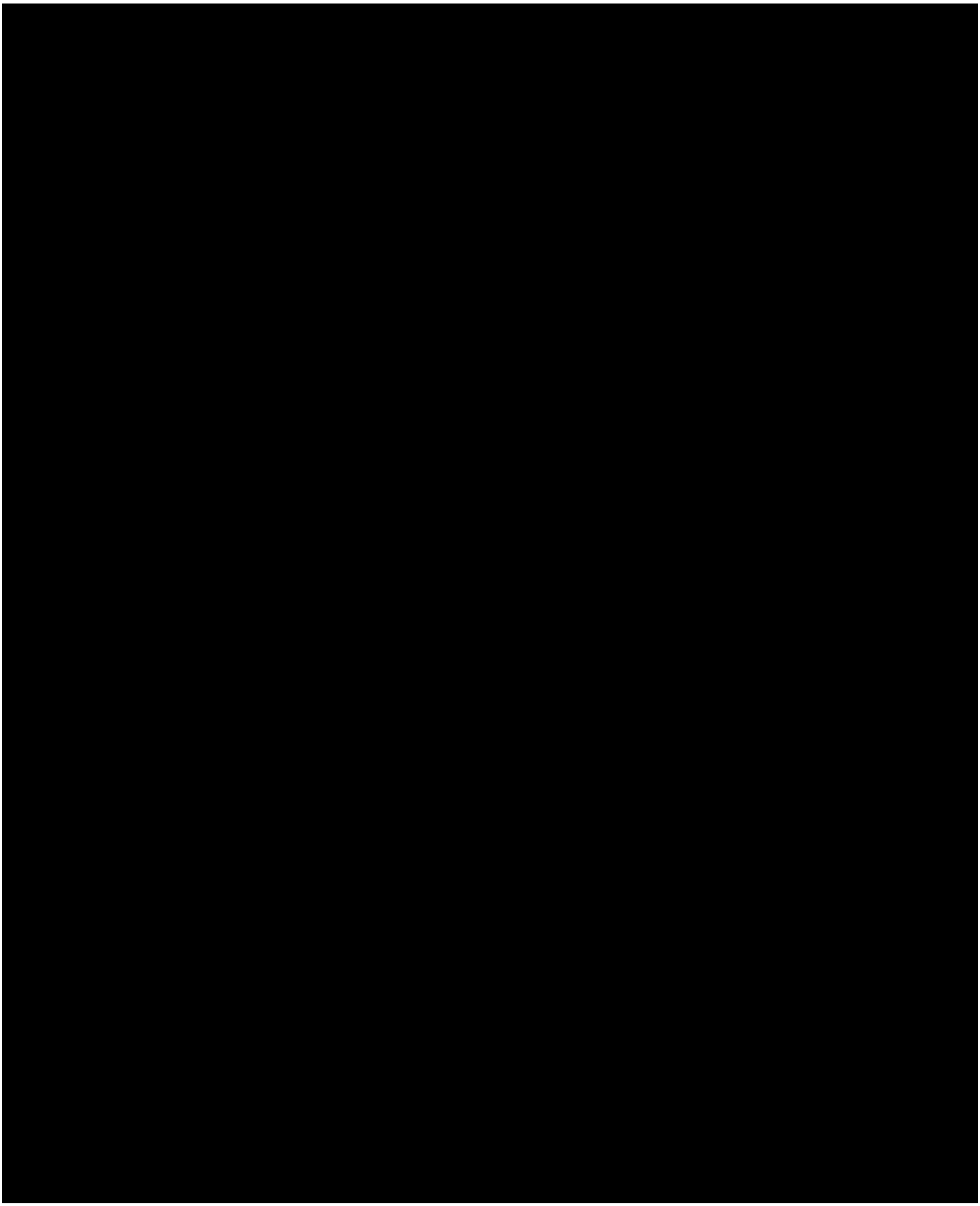
❑ **Pharmacokinetics Evaluations**

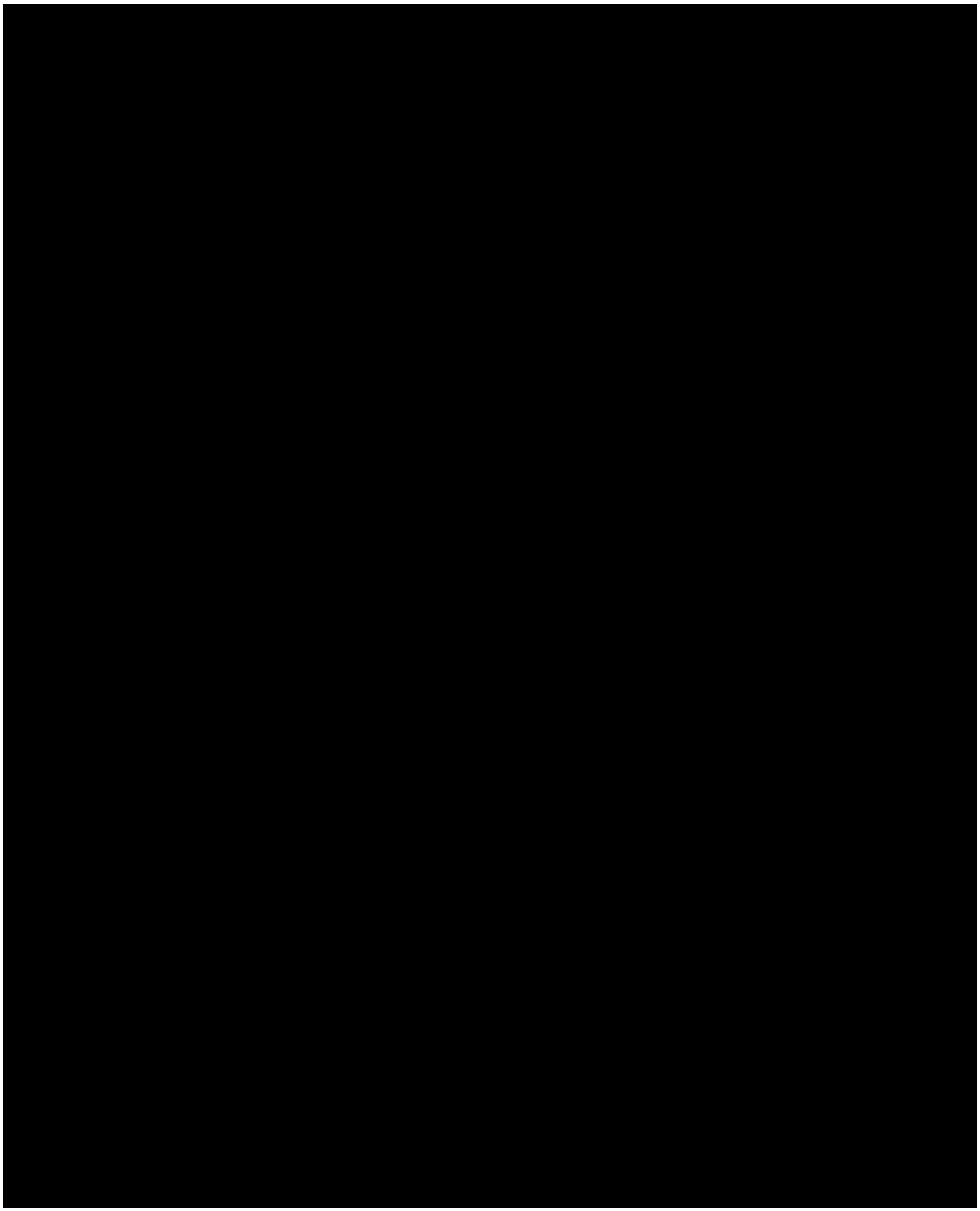
At V2 –V7, plasma specimens will be collected to assay for the presence of hSlo DNA by PCR. This data will be listed and presented descriptively. No PK analysis will be performed.

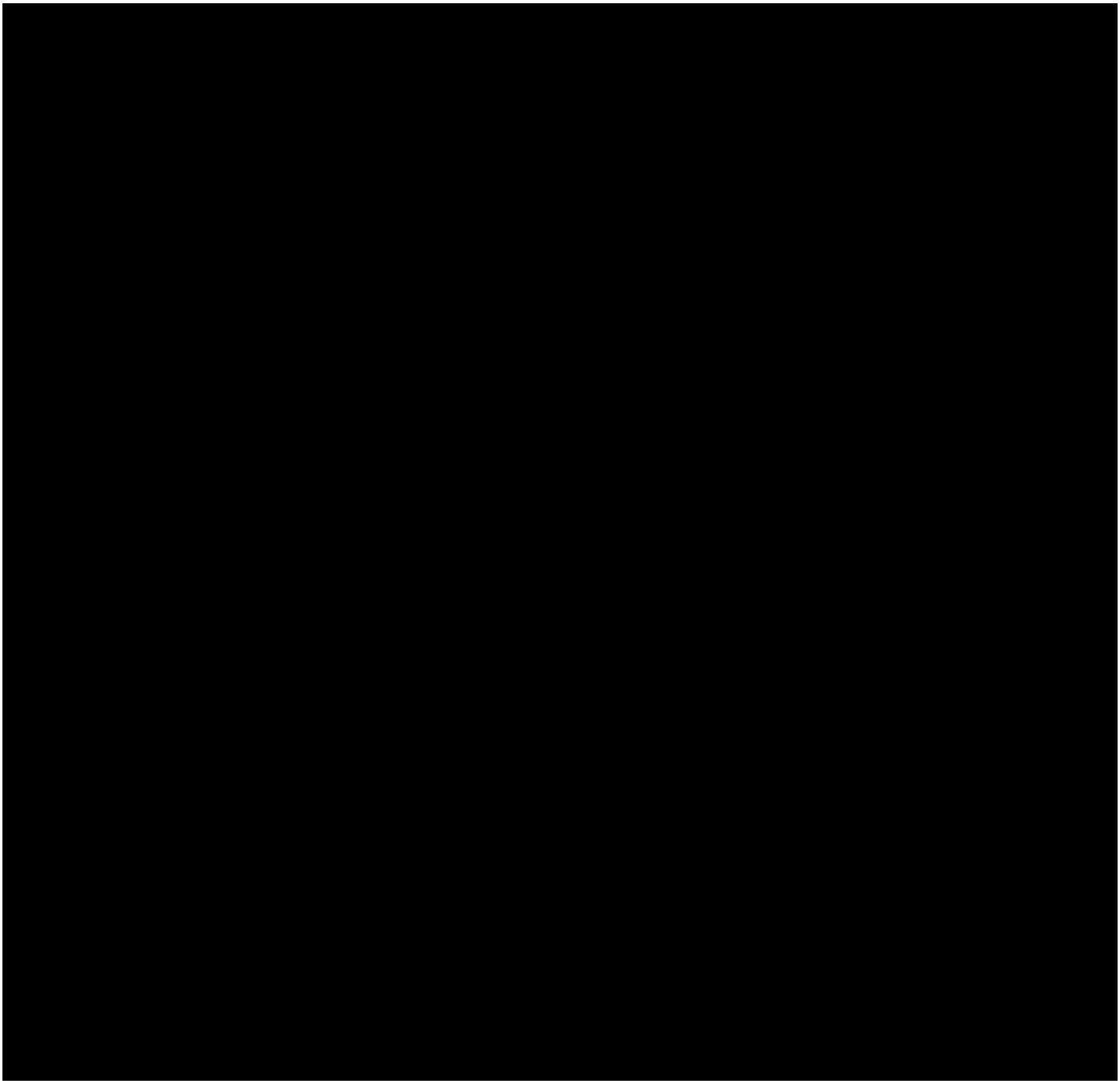
10. Listings, Tables and Figures











11. Software

SAS® Version 9.2 or higher will be used for all data analysis

12. Reference

- Final Kuwait protocol 9-15-14: A Double-blind, Placebo-controlled, Parallel Design, Randomized, Phase 2A Clinical Trial Evaluating the Potential Activity and Safety of hMaxi-K Gene Transfer in Males with Erectile Dysfunction
- Final ION protocol 01-Mar-16 version 1.2.pdf