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STATISTICAL ANALYSIS PLAN

PROTOCOL NO: BIOPIN 101

A Phase 1, placebo-controlled, Single-Ascending-Dose Study of BIOPIN 6 in Healthy Adults

Protocol Version No.: 6.0 **Version Date:** 7 March 2025

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DRUG DELIVERY COMPANY

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STATISTICAL ANALYSIS PLAN

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A Phase 1, placebo-controlled, Single-Ascending-Dose Study of BIOPIN 6 in Healthy Adults

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1. ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BAC	Blood alcohol concentration
CFR	Code of Federal Regulations
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common terminology criteria for adverse events
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDMS	Electronic Data Management System
EOS	End of study
F	Fahrenheit
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hr	Hour
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
µg	Microgram
min	Minutes
mL	Milliliter
mm	Millimeter
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class

2. INTRODUCTION

This statistical analysis plan (SAP) for Protocol No. BIOPIN 101, "A Phase 1, placebo-controlled, Single-Ascending-Dose Study of BIOPIN 6 in Healthy Adults" describes and expands upon the analytical plan presented in the protocol.

This document contains all planned analyses, reasons and justifications for these analyses for all study data. This plan also includes sample tables, figures, and listings that will be populated. The SAP will follow the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines as indicated in Topic E3 (Structure and Content of Clinical Study Reports), Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH.

The following sources were used in preparation of this SAP:

- Protocol # BIOPIN 101, Protocol Version No.: 5.0; Version Date: 28Jul2024
- ICH Guidance Topics E9, E3 and E8

3. CHANGE IN THE ANALYSIS PLAN

After the data were available for dose-level#2, it was determined to not proceed to a higher dose as the target exposure levels were achieved. Thus, the draft SAP was revised and finalized to reflect the analysis of the data collected from the first two planned cohorts.

4. PROTOCOL SUMMARY

4.1. Study Objectives

4.1.1. Primary

The primary objective of the study is to determine naltrexone and 6b-naltrexole pharmacokinetic parameters in subjects administered a single dose of BIOPIN 6 [BIOPIN 6 implants containing 4.8g (dose-level #1) or 9.6g (dose-level #2).

4.1.2. Secondary

Secondary objectives include determining the safety of BIOPIN 6 implants by assessing adverse events, incision/implant site local reactions, clinical laboratory data, and vital signs.

4.2. Study Design

Placebo-controlled study of 2 sequential cohorts receiving 4.8g or 9.6g of BIOPIN 6 implanted into a subcutaneous pocket in the upper abdominal wall. The placebo will be an implant consisting of the poly-d-l Lactic Acid and polycaprolactone contained in BIOPIN 6 without naltrexone. In each cohort, subjects will be randomized 6 (BIOPIN 6) vs 2 (placebo). At 12

weeks after implantation, the implant will be removed. The safety data for each cohort will be reviewed by the study team before the next cohort is entered into the study.

In accordance with the labelled adverse effects of naltrexone (Vivitrol), entrance criteria are designed to ensure that: subjects are not using opioids, are not using other drugs which in the presence of this opioid-receptor blocker might not be as rewarding as expected, do not have hepatic dysfunction, and do not have suicidal tendencies. After investigational product administration, subjects will be followed for adverse events, hepatotoxicity and reticulocytes in addition to other laboratory measures, suicidality/depression.

Because BIOPIN 6 contains poly-d-l Lactic Acid and polycaprolactone in addition to naltrexone and will be implanted into the subcutaneous tissue, other entrance criteria are not being intolerant of the poly-d-l Lactic Acid and polycaprolactone, not having a bleeding tendency, and not being prone to skin rashes or skin irritation.

The Protocol Timetable is shown below.

Protocol Timetable

Study Phase	Screening (days -28 to -2)	Day -1	Day 1 to Week 11[12]	Week 12 (and week 14)[11, 12]
Informed consent	X			
Demographic data [1]	X			
Medical history	X	X (update if needed)		
Physical exam [2]	X	X (update if needed)	Week 4 and 8	X
Weight/height	X			
Urine drugs of abuse screen[3]	X	X	Week 4 and 8	X
Alcohol breath test	X			
Naloxone challenge test	X	X		
Concomitant medications	X	X	Weekly	X
Serology[4]	X	X		
Birth Control Methods/Pregnancy Test[5]	X	X		
C-SSRS for suicidality	X	X	Weeks 4 and 8	X
HAM-D for depression	X	X	Weeks 2,4,6,8,10	X
Inclusion/exclusion criteria	X	X		
Randomization[6]		X		
Residential visits		Check in on day (-1)	Check out on Day 4 (72 hours postdose)	Week 12
Non-residential visits	X		Days 7 and 10, and Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Week 12 (week 14)
Study drug (Biopin or placebo) administration by implantation[6]			Day 1 (0 h): Insert BIOPIN implant	Remove BIOPIN implant (and week 14)[11]
Implant Tissue Assessment			At each residential and non-residential visit	Gross and microscopic descriptions and photos of each tissue capsule.

[1] Age, gender, and race/ethnicity
[2] Abbreviated exam
[3] Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, cannabinoids, phencyclidine, propoxyphene, methadone.
[4] Hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen, covid antigen
[5] Serum HCG test at screening; urine HCG test at day (-1. For postmenopausal females, a follicle stimulating hormone test will be performed during screening.
[6] Each dose cohort of 8 subjects randomized 6 active vs 2 placebo

Study Phase	Screening (days -28 to -2)	Day -1	Day 1 to Week 11[12]	Week 12 (and week 14)[11, 12]
Safety and tolerability:				
Adverse event recording	X		Predose, 8, 24, 48 and 72 hours postdose. Then weekly	X
Vital signs [7]	X		Predose, 8, 24, 48 and 72 hours postdose. Weeks 4 and 8.	X (pre and post explant)
12-lead ECG	X	X	Week 4 and 8	X (pre and post explant)
Clinical chemistries[8]	X		72 hours post dose; then weeks 4 and 8	X
Hematology[9]	X		72 hours post dose; then weeks 4 and 8	X
Coagulation[10]	X			
Pharmacokinetics (naltrexone and its major metabolite, 6-beta-naltrexol)				
Blood sampling (29 samples)			Predose. Hours 1, 3, 6, 12, 24, 48 and 72. Days 7 and 10. Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Week 12: pre-explant and 1, 3, 6, 12, 24 hrs after explant (as resident). 48,72, and 96 hrs (non resident).

[7] Heart rate (sitting), blood pressure (sitting), respiratory rate, oral temperature
[8] ALT, albumin, alkaline phosphatase, AST, bilirubin (total and direct), calcium, chloride, cholesterol, creatinine, GGT, glucose, phosphate, potassium, sodium, total protein, uric acid, and blood urea nitrogen (BUN).
[9] Hemoglobin, hematocrit, red blood cell count (RBC), reticulocytes, white blood cell count (WBC), platelets
[10] Fibrinogen, prothrombin time (PT), and partial thromboplastin time (PTT).
[11] Subjects return for a non-residential visit on week 14 for surgical evaluation of explantation site
[12] For non-resident days, window will be target day [Week 2 (Day 14), Week 3 (Day 21), etc.] +/- 3 days

5. STUDY ENDPOINTS

5.1. Pharmacokinetics

The following PK parameters will be determined for naltrexone and 6b-naltrexole:

AUC_t: Area under the plasma concentration-time curve from time 0 to the time (t) of last quantifiable concentration (Ct) calculated by the log-linear trapezoidal rule.

AUC_∞: Area under the plasma concentration-time curve from time 0 extrapolated to infinity. The terminal area from Ct to infinity was calculated by using the approximation as $Ct/\lambda z$ thus $AUC_\infty = AUC_t + Ct/\lambda z$.

C_{max}: The maximum observed plasma concentration.

t_{max}: The observed time to reach maximum plasma concentration.

λ_z: The terminal-phase exponential rate constant as calculated from the negative slope of the regression line for the terminal linear portion of the LN transformed plasma concentration versus time curve.

$t_{½}$: The apparent terminal exponential half-life, calculated as $\ln(2)/\lambda_z$.

5.2. Safety Endpoints

Safety endpoints will be analyzed over the entire treatment and follow-up period.

1. Adverse events (AEs) and serious adverse events (SAEs)
2. Vital signs
3. Physical examination of the nasal mucosa
4. Blood chemistries and hematology
5. Electrocardiogram (ECG) results
6. Suicidality: Frequency of subjects with suicidal ideation at any time during the treatment period using the Columbia-Suicide Severity Rating Scale (C-SSRS)
7. Depression: HAM-D17 Scores

6. DEFINITION OF ANALYSIS SETS

The study analysis populations will consist of the following:

Safety Analysis Set: All subjects who received an implant.

PK analysis set. All subjects who provided sufficient data to determine PK parameters will be included in this analysis set.

7. HYPOTHESES TO BE TESTED

There are no statistical hypotheses being tested in this study. All data will be presented as descriptive statistics.

8. SAMPLE SIZE CONSIDERATIONS

The primary endpoint is PK. The sample size of 6 evaluable drug-treated subjects per dose level is standard for PK studies.

9. DATA QUALITY ASSURANCE

Data quality assurance will start with training of clinical investigative staff on data collection and including an Electronic Data management System (EDMS) User Guide. The EDMS User Guide describes what data to collect and procedures for completion of electronic case report form (eCRFs.) Completed eCRFs will be reviewed by clinical monitors on a regular basis throughout the trial by comparison against the source documents.

Study data will come from the eCRFs and other data sources including an electronic file containing plasma concentrations for naltrexone and 6b-naltrexoleas well as the PK parameters. eCRFs for this study were created using an EDMS based on a Zelta by Merative Operating System. eCRFs were created using an established data dictionary for each variable including the field name, field type, field attributes, and coding for variables. Range checks, alpha-numeric requirements, and null/not null parameters were programmed as applicable. The back end database application is Oracle. Data entered into the EDMS system will be reviewed by Cognitive Research Corporation (CRC) clinical monitors and Fast-Track data managers. If incomplete or inaccurate data are found, the data will be queried in the system for site staff to address. The site will resolve data inconsistencies and errors using the EDMS with full audit trail of corrections being maintained within the system. Corrections and changes to the data will be reviewed by CRC clinical monitors and Fast-Track data managers.

Additional edit checks will be written to detect anomalies in the database. These checks will address inconsistencies (within visits, across visits), invalid/unusual values, missing values, and protocol violations. Edit checking will be validated on test data or actual clinical trial data. In addition to programmed edit checks, quality control examination of data will also be performed on reviews of data listings.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

For descriptive purposes, dichotomous and categorical variables will be presented as number of observations and percentages; continuous variables will be given as means, standard deviations (SD), median, minimum (min) and maximum (max). All data will be presented in listings. Table, listing, and figure shells are presented in Section 13. Data will be summarized by each of the 2 Biopin 6 treatment groups and by placebo control group.

10.2. Participant Accountability and Protocol Deviations

A summary will be prepared for the disposition of all consented subjects along with the reason(s) for early discontinuation. Reasons for not meeting the protocol eligibility criteria and protocol deviations will be presented as listings.

10.3. Demographics and Other Baseline Characteristics

Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared for the safety analysis set. Demographic characteristics (e.g., age, gender, race, and ethnicity), height, weight, and body mass index will be summarized. Blood alcohol levels, birth control methods, and pregnancy test results will be presented in a listing. Screening naloxone challenge tests vital signs and pupil diameter will be summarized for each timepoint including change from the predose value. Other signs of a response to naloxone (sneezing/coughing, yawning, lacrimation, rhinorrhea, shivering, restlessness, sweating, vomiting, gooseflesh) will be summarized by sign, timepoint and severity score at each timepoint. All of these data will also be presented in a listing by subject. Other listings will include medical history terms and physical examination findings.

10.4. Drugs of Abuse

The numbers and percentages of subjects with a positive urine drug test at each timepoint by treatment group will be presented.

10.5. Study Treatments

The number and type of implant (Biopin 6 or placebo) will be presented by study group. A listing including this data as well as the distance of the incision to the closest palpable edge of each implant along with the date and time of the implant and if problems were encountered will also be provided.

Visual evaluation of the incision site and gross descriptions and microscopic descriptions of each implant at the time of implant explant will also be provided in a listing. Summaries of the severity grade for the visual inspections including wound infection, bleeding, and scarring, and the presence of absence of paresthesia, perforation, implant migration, implant extrusion, wound dehiscence, and implant fragmentation will also be summarized.

10.6. PK Analysis

Concentration-time profiles will be presented graphically for each subject and by mean ± standard error of the mean (SEM) by Biopin 6 group by nominal time point for naltrexone and 6b-naltrexole. The concentration-time profiles will be evaluated by non-compartmental analysis to determine PK parameters. Actual sample times will be utilized for calculations. Calculations of parameters will be performed with Phoenix WinNonLin 8.4 (Certara, Radnor, PA). The elimination rate constants (λ_z) will be estimated from the terminal log-linear decline in plasma concentrations and $t_{½}$ calculated as $\ln(2)/\lambda_z$. Area under the plasma concentration curves will be determined till the last time of a quantifiable plasma concentration (AUC_t) by the log/linear trapezoidal rule and to infinity (AUC_∞) based on the last plasma concentration (Ct) and λ_z . The value of t_{max} will be the observed time of the highest plasma concentration and C_{max} would be the plasma concentration at that time. Mean, SD, geometric mean, median, minimum and maximum will be presented for each PK parameter.

10.7. Safety Analysis

10.7.1. Adverse Events

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be grouped by system, organ, and class (SOC) and preferred term (PT) designation. The severity, frequency, and relationship of AEs to investigational product will be presented by SOC and PT groupings. Listings of each individual AE including start date, stop date, severity, relationship to IP, outcome, action taken (including any treatment administered), and duration will be provided.

Every AE will be assessed for whether or not it qualifies as an SAE. All SAEs will be categorized and listed according to the following categories: Congenital Anomaly or Birth Defect; Persistent or Significant Disability/Incapacity; Results in Death; Requires or Prolongs Hospitalization; Other Medically Important Serious Event; or Life-Threatening. For deaths, the date and cause of death will be collected and listed. For hospitalizations, the dates of admission and release (discharge) will be collected and listed.

Each AE (based on PT) will be counted once only for a given study subject. If the same AE occurred on multiple occasions, the highest severity will be assumed. Thus, study subjects are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE. C-SSRS reports of suicidality or suicidal ideation will be reported as AEs and analyzed as AEs if the investigator determines after an interview with the subject, that the responses are consistent with suicidal ideation or attempt.

10.7.2. Implant Visual Inspection

The incision site will be examined at each visit post implant. At each timepoint for each group, the severity grades for wound infection, bleeding, and scarring, and the presence or absence of paresthesia, perforation, implant migration, implant extrusion, and wound dehiscence will also be summarized.

10.7.3. Suicidality and Depression

The number and percentage of subjects that endorse suicidal ideation and suicide attempt at any time during the study will be presented based on the responses to the Columbia Suicide Severity Rating Scale (CSSR-S). For HAM-D17 scores, the mean, SD, change from Day -1, median, and range of all values at each time point will be presented in a summary table. The number and percentages of subjects with scores greater than 7, that is considered to be indicative of clinical depression will be presented for all timepoints.

9.7.4 Clinical Laboratory

Descriptive statistics will be generated for all tests performed at screening and at each clinic visit. If a laboratory analysis is repeated, the last measurement performed prior to the clinic visit will be used in the summary statistics for that clinic visit. If an unscheduled clinical laboratory visit occurs prior to a scheduled visit that is missed due to dropout, then the unscheduled visit will be used in the summary statistics for the missed scheduled clinical visit. If an unscheduled clinical laboratory visit occurs between two scheduled clinical visits, then the data from the unscheduled visit will only be presented in the listings and not in summary statistics. In addition, at each post-randomization clinic visit descriptive statistics for change from baseline will be generated for clinical chemistry and hematology tests. Laboratory values will be plotted as mean ± standard error over time. All laboratory measurements will be presented in the listings including an assessment if the laboratory value is considered within normal limits or is not clinically significant or is clinically significant.

The number and percentage of positive urine drug tests and pregnancy tests for screening visits and all treatment and follow-up visits will be tabulated. Results of all urine drug tests and pregnancy tests will be presented in the listings. The percentage of subjects with a positive urine drug test at any time post start of treatment will also be presented by test type and treatment group.

9.6.3 Vital Signs

Vital signs will be presented as summary statistics and change from baseline. Values will be graded in accordance with the common criteria for adverse events (CTC-AE) version 5. The number and percentage of subjects with a vital sign measurements meeting grade 2 or greater criteria will be summarized by treatment group and CTC-AE grade. The percentage of ECG results considered abnormal and clinically significant will be presented as numbers and percentages for each timepoint. Vital signs and ECG results for all visits will be presented in the listings.

10.7.4. Concomitant Medications, Medical History, and Pregnancy Tests

Prior and concomitant medications will be presented in a listing including the verbatim term, dose, frequency, start and stop dates, and indication.

11. TABLES FOR SAFETY MONITORING

On completion of each cohort, the following tables will be prepared and provided to the Safety Monitoring Committee. Listings will also be provided on request.

12. VALIDATION OF PROGRAMMING CODE

All SAS codes used to generate tables and listings will be validated and reviewed before being finalized. The validation process will be used to determine that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Qualified personnel who have not previously been involved in the production of the original programming codes will perform the validation procedures. Methods of validation include independent programming and comparison to data listings. Tables will be reviewed for accuracy, consistency with this plan, consistency within tables, and consistency with corresponding output. Once validation is complete, a quality control reviewer will perform a final review of the documents for accuracy and consistency. Upon completion of validation and quality review procedures, all documentation will be collected and filed in the study documentation files at Fast-Track.

13. TABLES, LISTINGS, AND FIGURE SHELLS

LIST OF TABLES

13.1. Table Shells

13.1.1. Screening and Baseline Assessments

Table 1: Subject Disposition - All Consented Subjects

	Treatment Group			
	Biopin 6 1 implants	**Biopin 6 2 implants**	**Placebo 1 to 2 implants**	**All subjects**
	n (%)	**n (%)**		**n (%)**
Subjects Consented				xxx
Subjects Not Eligible				xxx (xx.x%)
Subjects Randomized	xx	xx	xx	xx
Subjects Randomized but Did Not Receive an Implant	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Subjects Randomized and Received an Implant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Completed Subjects	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Subjects with early explant of implant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Subjects who withdrew from the study early	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for early withdrawal				
Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to follow up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Physician decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pregnancy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Protocol deviation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Study termination by sponsor	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Withdrawal of consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other reason	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 2: Demographic Characteristics

	Biopin 6 1 implant	**Biopin 6 2 implants**	**Placebo 1 to 2 implants**	**All subjects**
Characteristic	**(N=xx)**	**(N=xx)**	**(N=xx)**	**(N=xx)**
Age (years)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)	(xx-xx)
Gender at Birth				
N				
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Race				
N	xx	xx	xx	xx
White	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
African-American or Black	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Asian	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Native Hawaiian or Other Pacific Islander	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
American Indian or Alaskan Native	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
More than one race or other race	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unknown or not reported	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ethnicity				
N	xx	xx	xx	xx
Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not reported	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Height (cm)				
N	xx.x	xx.x	xx.x	xx.x
Mean (SD)	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Min-Max	xx.x	xx.x	xx.x	xx.x

Table 2: Demographic Characteristics (Continued)

Characteristic	Biopin 6 1 implant (N=xx)	Biopin 6 2 implants (N=xx)	Placebo 1 to 2 implants (N=xx)	All subjects (N=xx)
Weight (kg)				
N	xx.x	xx.x	xx.x	xx.x
Mean (SD)	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Min-Max	xx.x	xx.x	xx.x	xx.x
Body Mass Index (kg/m^2)				
N	xx.x	xx.x	xx.x	xx.x
Mean (SD)	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Min-Max	xx.x	xx.x	xx.x	xx.x

Table 3: Naloxone Challenge Tests Vital Signs and Pupil Diameters – Screening

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Heart rate (bpm) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Heart rate (bpm) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Heart rate (bpm) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Heart rate (bpm) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Heart rate (bpm) Post Challenge			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diastolic Blood Pressure (mmHg) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Diastolic Blood Pressure (mmHg) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Diastolic Blood Pressure (mmHg) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Diastolic Blood Pressure (mmHg) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Diastolic Blood Pressure (mmHg)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Systolic Blood Pressure (mmHg) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Systolic Blood Pressure (mmHg) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Systolic Blood Pressure (mmHg) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Systolic Blood Pressure (mmHg) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Systolic Blood Pressure (mmHg)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Respiratory Rate (breaths/min) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Respiratory Rate (breaths/min) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Respiratory Rate (breaths/min) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Respiratory Rate (breaths/min) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Respiratory Rate (breaths/min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin Temperature (°F) (-30 min)			
N	xx	xx	xx

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Skin Temperature (°F) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Skin Temperature (°F) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Skin Temperature (°F) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Skin Temperature (°F)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pupil Diameter (mm) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Pupil Diameter (mm) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Pupil Diameter (mm) (30 min)			
N	xx	xx	xx

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)

Table 4: Naloxone Challenge Tests Vital Signs and Pupil Diameters – Day -1

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Heart rate (bpm) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Heart rate (bpm) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Heart rate (bpm) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Heart rate (bpm) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Heart rate (bpm) Post Challenge			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diastolic Blood Pressure (mmHg) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Diastolic Blood Pressure (mmHg) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Diastolic Blood Pressure (mmHg) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Diastolic Blood Pressure (mmHg) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Diastolic Blood Pressure (mmHg)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Systolic Blood Pressure (mmHg) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Systolic Blood Pressure (mmHg) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Systolic Blood Pressure (mmHg) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Systolic Blood Pressure (mmHg) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Systolic Blood Pressure (mmHg)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Respiratory Rate (breaths/min) (-30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Respiratory Rate (breaths/min) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Respiratory Rate (breaths/min) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Respiratory Rate (breaths/min) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Respiratory Rate (breaths/min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin Temperature (°F) (-30 min)			
N	xx	xx	xx

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Skin Temperature (°F) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Skin Temperature (°F) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Skin Temperature (°F) (30 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Change in Skin Temperature (°F)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pupil Diameter (mm) (-15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Pupil Diameter (mm) (15 min)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)
Pupil Diameter (mm) (30 min)			
N	xx	xx	xx

Assessment	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min-Max	(xx-xx)	(xx-xx)	(xx-xx)

Table 5: Naloxone Challenge Tests Objective Signs- Screening

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Sneezing/Coughing (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sneezing/Coughing (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sneezing/Coughing (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yawns (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yawns (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yawns (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lacrimation (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lacrimation (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lacrimation (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rhinorrhea (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rhinorrhea (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rhinorrhea (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Shivering (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Shivering (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Shivering (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Restlessness (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Restlessness (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Restlessness (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sweating (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sweating (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sweating (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vomiting (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vomiting (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vomiting (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gooseflesh (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gooseflesh (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gooseflesh (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mydriasis (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mydriasis (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 6: Naloxone Challenge Tests Objective Signs- Day -1

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Sneezing/Coughing (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sneezing/Coughing (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sneezing/Coughing (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yawns (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yawns (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yawns (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lacrimation (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lacrimation (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lacrimation (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rhinorrhea (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rhinorrhea (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rhinorrhea (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Shivering (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Shivering (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Shivering (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Restlessness (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Restlessness (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Restlessness (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sweating (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sweating (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sweating (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vomiting (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vomiting (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vomiting (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gooseflesh (-15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gooseflesh (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gooseflesh (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mydriasis (+15 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mydriasis (+30 min)			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

13.1.2. Treatment Records

Table 7: Study Treatment –Implants

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Distance to incision from palpable edge of implant 1			
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Min - Max	xx - xx	xx - xx	xx - xx
Distance to incision from palpable edge of implant 2			
Mean (SD)		xx (xx.x)	xx (xx.x)
Min - Max		xx - xx	xx - xx
Distance to incision from palpable edge of implant 3			
Mean (SD)			xx (xx.x)
Min - Max			xx - xx

Table 8: Study Treatment –Explants Inspection at Time of Explant

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Duration of Implant period (days)			
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Min - Max	xx - xx	xx - xx	xx - xx
Wound Infection			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bleeding			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Duration of Implant period (days)			
Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Min - Max	xx - xx	xx - xx	xx - xx
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Scarring			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Paresthesia			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Perforation			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Implant Migration			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Implant Extrusion			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Wound Dehiscence			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Implant Fragmentation			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

13.1.3. Pharmacokinetics

Table 9: Naltrexone Plasma Concentrations Over Time

		Biopin 6: 1 implant					Biopin 6: 2 implants				
Relative Timepoint	**Nominal Timepoint (Week)**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**
1hr post dose	0.006	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
3hr post dose	0.018	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
6hr post dose	0.036	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
12hr post dose	0.071	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
24hr post dose	0.143	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
48hr post dose	0.286	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
72hr post dose	0.429	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Day 10	1.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 2	1.429	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Day 7	2.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 3	3.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 4	4.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 5	5.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 6	6.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 7	7.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 8	8.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 9	9.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 10	10.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 11	11.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Pre-explant	12.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x

		Biopin 6: 1 implant					Biopin 6: 2 implants				
Relative Timepoint	**Nominal Timepoint (Week)**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**
1hr post-explant	12.006	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
3hr post-explant	12.018	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
6hr post-explant	12.036	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
12hr post-explant	12.071	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
24hr post-explant	12.143	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
48hr post-explant	12.286	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
72hr post-explant	12.429	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
96hr post-explant	12.571	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x

Table 10: 6 Beta-Naltrexol Plasma Concentrations Over Time

		Biopin 6: 1 implant					Biopin 6: 2 implants				
Relative Timepoint	**Nominal Timepoint (Week)**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**
1hr post dose	0.006	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
3hr post dose	0.018	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
6hr post dose	0.036	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
12hr post dose	0.071	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
24hr post dose	0.143	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
48hr post dose	0.286	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
72hr post dose	0.429	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Day 10	1.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 2	1.429	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Day 7	2.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 3	3.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 4	4.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 5	5.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 6	6.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 7	7.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 8	8.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 9	9.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 10	10.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Week 11	11.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
Pre-explant	12.000	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
1hr post-explant	12.006	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x

		Biopin 6: 1 implant					Biopin 6: 2 implants				
Relative Timepoint	**Nominal Timepoint (Week)**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**	**N**	**Mean (ng/mL)**	**SD (ng/mL)**	**SEM (ng/mL)**	**% CV**
3hr post-explant	12.018	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
6hr post-explant	12.036	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
12hr post-explant	12.071	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
24hr post-explant	12.143	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
48hr post-explant	12.286	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
72hr post-explant	12.429	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x
96hr post-explant	12.571	x	xx.x	x.xx	x.xx	xx.x	x	xx.x	x.xx	x.xx	xx.x

Table 11: Pharmacokinetic Parameters

	Biopin 6 1 implant	**Biopin 6 2 implants**
Parameter	**(N=xx)**	**(N=xx)**
$C_{max\ (ng/mL)}$		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x
Median	xx	xx
Min - Max	xx-xx	xx-xx
$t_{max\ (hr)}$		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x
Median	xx	xx
Min - Max	xx-xx	xx-xx
AUC_{0-4} (h*ng/mL)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x
Median	xx	xx
Min - Max	xx-xx	xx-xx
AUC_{0-8} (h*ng/mL)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x
Median	xx	xx
Min - Max	xx-xx	xx-xx
AUC_{0-last} (h*ng/mL)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x
Median	xx	xx
Min - Max	xx-xx	xx-xx
AUC_{∞} (h*ng/mL)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x

	Biopin 6 1 implant	**Biopin 6 2 implants**
Parameter	**(N=xx)**	**(N=xx)**
Median	xx	xx
Min - Max	xx-xx	xx-xx
λ_z		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x
Median	xx	xx
Min - Max	xx-xx	xx-xx
$t_{½\ (hr)}$		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Geometric mean	xx.x	xx.x
Median	xx	xx
Min – Max	xx-xx	xx-xx

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Table 12: Overall Summary of Adverse Events

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Number of AEs	xx	xx	xx
Number of SAEs	xx	xx	xx
Number (%) of subjects with at least one AE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number (%) of subjects with at least one SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number (%) of subjects with at least one AE related[2] to study product	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of AEs by severity			
Mild	xx (x.x%)	xx (x.x%)	xx (x.x%)
Moderate	xx (x.x%)	xx (x.x%)	xx (x.x%)
Severe	xx (x.x%)	xx (x.x%)	xx (x.x%)
Life-threatening	xx (x.x%)	xx (x.x%)	xx (x.x%)
Number of AEs by relationship to study product			
At least possibly related	xx (x.x%)	xx (x.x%)	xx (x.x%)
Unrelated	xx (x.x%)	xx (x.x%)	xx (x.x%)

Table 13: Number and Percentage of Subjects with Adverse Events

MedDRA System Organ Class/ Preferred Term	Biopin 6 1 implant (N=xx)	Biopin 6 2 implants (N=xx)	Placebo 1 to 2 implants
- Any Adverse Events -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC			
- Overall -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Percentages are based on the total number of subjects, as given in the column heading.
Multiple occurrences of a specific adverse event for a subject are counted once in the frequency for the adverse event. Likewise, multiple occurrences of adverse events within a specific preferred term for a subject are counted once in the frequency for the preferred term.
[1] Fisher's exact test
Programmer's Notes: Order System Organ Class alphabetically and preferred term alphabetically within System Organ Class.

Table 14: Summary of Subjects with Adverse Events by Severity and Relationship – Biopin 6 – 1 Implant

Number of Subjects (%) (N=x)												
		Mild		Moderate		Severe		Life-threatening		All Grades		
SOC	MedDRA PT	R	NR	R	NR	R	NR	R	NR	R	NR	R + NR
		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Events are counted once per subject at the highest severity grade and closest relationship to the investigational product. R= related to investigational product (possibly, probably, definitely). NR = not related to investigational product (unrelated, unlikely).

Table 15: Summary of Subjects with Adverse Events by Severity and Relationship – Biopin 6 – 2 Implants

Number of Subjects (%) (N=x)												
		Mild		Moderate		Severe		Life-threatening		All Grades		
SOC	MedDRA PT	R	NR	R	NR	R	NR	R	NR	R	NR	R + NR
		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Events are counted once per subject at the highest severity grade and closest relationship to the investigational product. R= related to investigational product (possibly, probably, definitely). NR = not related to investigational product (unrelated, unlikely).

Table 16: Summary of Subjects with Adverse Events by Severity and Relationship – Placebo

Number of Subjects (%) (N=x)												
		Mild		Moderate		Severe		Life-threatening		All Grades		
SOC	MedDRA PT	R	NR	R	NR	R	NR	R	NR	R	NR	R + NR
		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Events are counted once per subject at the highest severity grade and closest relationship to the investigational product. R= related to investigational product (possibly, probably, definitely). NR = not related to investigational product (unrelated, unlikely).

Table 17: Number and Percentage of Subjects with Adverse Events Occurring in ≥ 5% of Subjects

MedDRA SOC/	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Preferred Term	**(N=xx)**	**(N=xx)**	**(N=xx)**
SOC			
- Overall -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Percentages are based on the total number of subjects, as given in the column heading.
Multiple occurrences of a specific adverse event for a subject are counted once in the frequency for the adverse event. Likewise, multiple occurrences of adverse events within a specific preferred term for a subject are counted once in the frequency for the preferred term. At least 5% occurring in either arm to be included in the table.
[1] Fisher's Exact test
Programmer's Notes: Order System Organ Class alphabetically and preferred term alphabetically within System Organ Class.

Table 18: Number and Percentage of Subjects with Adverse Events by Maximum Severity

MedDRA SOC/	Biopin 6 -1 implant				Biopin 6 -2 implants			
Preferred Term	(N=xx)				(N=xx)			
	Mild	Moderate	Severe	Life-threatening	Mild	Moderate	Severe	Life-threatening
- Any Adverse Events -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC								
- Overall -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

MedDRA SOC/	Placebo 1 to 2 implants			
Preferred Term	(N=xx)			
	Mild	Moderate	Severe	Life-threatening
- Any Adverse Events -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SOC				
- Overall -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Percentages are based on the total number of subjects, as given in the column heading.
Multiple occurrences of a specific adverse event for a subject are counted once in the frequency for the adverse event. Likewise, multiple occurrences of adverse events within a specific preferred term for a subject are counted once in the frequency for the preferred term.
Programmer's Notes: Order System Organ Class alphabetically and preferred term alphabetically within System Organ Class.

Table 19: Number and Percentage of Subjects with Adverse Events Leading to Discontinuation of Study

MedDRA SOC/	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Preferred Term	**(N=xx)**	**(N=xx)**	**(N=xx)**
SOC			
- Overall -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Percentages are based on the total number of subjects, as given in the column heading.
Multiple occurrences of a specific adverse event for a subject are counted once in the frequency for the adverse event. Likewise, multiple occurrences of adverse events within a specific preferred term for a subject are counted once in the frequency for the preferred term.
Programmer's Notes: Order System Organ Class alphabetically and preferred term alphabetically within System Organ Class.

Table 20: Number and Percentage of Subjects with Adverse Events Leading to Early Explant

MedDRA SOC/	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Preferred Term	**(N=xx)**	**(N=xx)**	**(N=xx)**
SOC			
- Overall -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Notes: Percentages are based on the total number of subjects, as given in the column heading.
Multiple occurrences of a specific adverse event for a subject are counted once in the frequency for the adverse event. Likewise, multiple occurrences of adverse events within a specific preferred term for a subject are counted once in the frequency for the preferred term.
Programmer's Notes: Order System Organ Class alphabetically and preferred term alphabetically within System Organ Class.

Table 21: Incision Site Visual Inspection

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 3 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Repeat for each visit: Day 1, 2, 3, 4, 7, 10, Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12			
Wound Infection			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bleeding			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Scarring			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Paresthesia			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Perforation			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Implant Migration			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Implant Extrusion			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Wound Dehiscence			
N	xx	xx	xx
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 22: Suicidal Ideation or Suicide Attempt (CSSR-S)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Repeat for each visit: Screening, Day -1, Weeks 4, 8, and 12			
Suicidal Ideation			
n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Suicide Attempt			
n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 23: HAM-D17 Scores

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Repeat for each visit: Screening, Day -1, Weeks 2, 4, 6, 8, and 12			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
Min - Max	xx-xx	xx-xx	xx-xx

Table 24: HAM-D17 Number and Percentage of Patients with Scores Indicative of Clinical Depression (Scored > 7)

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Assessment	**(N=xx)**	**(N=xx)**	**(N=xx)**
Repeat for each visit: Screening, Day -1, Weeks 4, 8, and 12			
n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 25: Summary of Blood Chemistries

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Repeat for each visit: Screening, Day -1, Day 3, Weeks 4 and 8			
Test Name (units)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min - Max	xx-xx	xx-xx	xx-xx
Change from baseline at Day -1, Day 3, Weeks 4 and 8			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min - Max	xx-xx	xx-xx	xx-xx

Programmers note: table will include alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin (total and direct), calcium, chloride, cholesterol, creatinine, GGT, glucose, phosphate, potassium, sodium, total protein, uric acid, and BUN.

Table 26: Summary of Hematology Tests

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Repeat for each visit: Screening, Day -1, Day 3, Weeks 4 and 8			
Test Name (units)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min - Max	xx-xx	xx-xx	xx-xx
Change from baseline at Day -1, Day 3, Weeks 4 and 8			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min - Max	xx-xx	xx-xx	xx-xx

Programmers note: Hemoglobin, hematocrit, red blood cell count (RBC), reticulocytes, white blood cell count (WBC), and platelets.

Table 27: Summary of Coagulation Tests at Screening

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
	(N=xx)	(N=xx)	(N=xx)
Repeat for each visit: Screening, Day -1, Day 3, Weeks 4 and 8			
Test Name (units)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min - Max	xx-xx	xx-xx	xx-xx

Programmers note: Fibrinogen, prothrombin time (PT), and partial thromboplastin time (PTT).

Table 28: Summary of Positive Urine Drug Tests

	Number positive (%)		
	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Test	(N=xx)	(N=xx)	(N=xx)
Timepoints include: Screening, Day -1, Weeks 4, 8, and 12			
Amphetamine	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Barbiturates	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Benzodiazapines	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cocaine	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Opiates	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
cannabinoids	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
phencyclidine	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
propoxyphene	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
methadone	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 29: Summary of Vital Signs

	Biopin 6 1 implant	**Biopin 6 2 implants**	**Placebo 1 to 2 implants**
	(N=xx)	**(N=xx)**	**(N=xx)**
Repeat for each visit: Screening, Day -1, Day 1 predose, then 8, 24, 48, and 72 hours post dose, then Weeks 4 and 8			
Test Name (units)			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min - Max	xx-xx	xx-xx	xx-xx
Change from baseline at Day 1 predose, then 8, 24, 48, and 72 hours post dose, then Weeks 4 and 8			
N	xx	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min - Max	xx-xx	xx-xx	xx-xx

Programmers note: vital signs include heart rate (sitting), blood pressure (sitting), respiratory rate, oral temperature

Table 30: Summary of ECG Results

	Biopin 6 1 implant	Biopin 6 2 implants	Placebo 1 to 2 implants
Result	**(N=xx)**	**(N=xx)**	**(N=xx)**
Screening			
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Not Clinically Significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Clinically Significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other time points include Day -1, Weeks 4 and 8			
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Not Clinically Significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal, Clinically Significant	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

13.2. Listing Shells

Redacted

13.3. Figure Shells

LIST OF FIGURES

Figure 1: Mean (SD) Chemistry Values Over Time

X-axis – Days – Y Axis – mean standard deviation for each chemistry value over time – all 3 groups

Figure 2: Mean (SD) Hematology Values Over time

X-axis – Days – Y Axis – mean standard deviation for each hematology value over time – all 3 groups

Figure 3: Mean (SD) Vital Signs Over Time

X-axis – Days – Y Axis – mean standard deviation for each vital sign value over time – all 3 groups

Figure 4: Mean (SEM) Plasma Concentrations Over Time

X-axis – Days – Y Axis – mean standard error of the mean for each plasma concentrations of naltrexone and 6b-naltrexol values (on separate graphs) over time plotted on linear and log scales – 2 groups

Figure 5: Individual Subjects Plasma Concentrations Over Time

X-axis – Days – Y Axis – naltrexone and 6b-naltrexol plasma concentrations for each subject