STUDY DOCUMENT COVER PAGE

Official Title: Study of the BIOPIN 6 Naltrexone Implant in Healthy Adults

NCT Number: NCT06216132

Unique Protocol ID: BIOPIN101

Document Type: Protocol

Document Date: February 27, 2026

Protocol Number: BIOPIN 101

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

Sponsor	DRUG DELIVERY COMPANY 26627 PEMBERTON DRIVE SALISBURY, MD 21801 scohen@rvaf.com
Sponsor's Representative	Dr. Steven Cohen, MD 265 8th Ave NE St. Petersburg, Florida 33701 scohen@rvaf.com
Principal Investigator	Dr. Todd Bertoch 650 E 4500 S, Suite 100 Salt Lake City, UT 84107 t.bertoch@cenexel.com
Clinical Trial Site	JBR Clinical Research 650 E 4500 S Suite 100 Salt Lake City, UT 84107 801-261-2000
Implant Surgeon	Dr. Scott Leckman Dr. Darrin Hansen
Original Protocol Date:	01Jan2024
Version Number:	5.0
Version Date:	28Jun2024

Clinical Laboratories and Other Departments/Institutions Involved in the Trial

Clinical Laboratory	Quest Diagnostics 3489 W 2100 S, Suite 200 West Valley City, UT 84119 801-978-2000
Bioanalytical Laboratory (pharmacokinetic samples)	Aliri Bioanalysis 1121 East 3900 South, Suite C-110 Salt Lake City, Utah 84124 United States of America 801-293-2358 shomith.mondal@aliribio.com
Clinical Pharmacologist	Gina Patel, PhD, MPharm Patel Kwan Consultancy LLC 847-830-5037
Biostatistician	Jeff Finman, Ph.D., Cognitive Research Corporation 200 Central Avenue, Suite 1200, St. Petersburg, FL 33701 727-897-9000 jfinman@cogres.com
Data Management Center	Thomas J. Hochadel, Pharm.D. Cognitive Research Corporation 200 Central Avenue, Suite 1200, St. Petersburg, FL 33701 727-897-9000 tomhochadel@cogres.com
Institutional Review Board	Advarra 6100 Merriweather Dr., Suite 600, Columbia, MD 21044 410-884-2900 Jennifer.Owen@advarra.com

SUMMARY OF CHANGES

Version Number	Brief Description of Changes	Page(s)/Sections Affected	Date
Original Protocol V1.0		N/A	01Jan2024
Version 2.0	• Sponsor address updated • Clinical Laboratory, Bioanalytical Laboratory, and Clinical Pharmacologist updated per Administrative Letter #1 • Summary of Changes added • Protocol Timetable (2.2) and footnotes updated • Removal of prior product information • Update to progression of cohort information • Update to IP accountability following study completion • Inclusion/Exclusion Criteria numbered • Clarification on definition of a completed subject • Clarification of Implant Assessment • Other minor edits	1, 28 2 3 8, 9 20 27 28 29-31 32 36 Throughout	08Apr2024
Version 3.0	• Total number of PK samples to be collected • Clarification for Exclusion criteria #2 and #9 • Additional language regarding withdrawn subjects • Clarification on vital signs at Screening visit	9, 39 31 33 36	20May2024

	• Clarification on collection of C-SSRS time frames at Screening • Update of PK collection and storage information • Update to who can determine AE relationship • Modification to language regarding what labs and vital signs constitute AEs • Update on SAE reporting timeframes • Update to SAE contact • Other minor edits	37 39 43 44 45, 47 45 Throughout	
Ver 4	• Clarifications on pregnancy, alcohol breathalyzer, EKG tests	9	13Jun2024
	• Clarification on CSSR and HAMD analyses	40	
	• Concise statement of anesthesia in appendices A and B	55, 67	
	• Specification of scoring scale for Naloxone Challenge Test	71-72	
	• Other minor edits	throughout	
Ver 5	• increased the SBP Exclusion criterion from >140mmHg to >150mmHg	Section 7.4, Exclusion criterion #2 (page 32).	28Jun2024
	• increased Vital Sign assessments between weeks 1-to-11 from "weeks 4 and 8" to "Days 7 and 10. and Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11"	Section 2.2 (Protocol Timetable), page 11. Section 8.3, page 38.	
	• Deleted "local" from Inclusion Criterion #8	Section 7.3, Inclusion criterion #8	

	• Other minor edits: delete serology on day (-1)	Throughout	

1. Investigator's Agreement

"I have received and read the Investigator's Brochure for BIOPIN 6. I have read the BIOPIN 6 101 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol."

Printed Name of Investigator: Dr. Todd Bertoch

Signature: _____

Date: _____

2. SYNOPSIS

Name of Sponsor: DRUG DELIVERY COMPANY
26627 PEMBERTON DRIVE
SALISBURY, MD 21801

Name of Investigational Product:

BIOPIN 6

Name of Active Ingredient:

Naltrexone

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

Study Center: JBR Clinical Research

Principal Investigator: Dr. Todd Bertoch

Phase of development: 1

2.1 Objectives:

Primary:

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), 9.6g (dose-level #2), or 14.4g (dose-level #3) naltrexone].

Secondary:

Adverse events (AEs), clinical laboratory values.

Methodology:

The study is divided into an Outpatient Screening Period, a Residency period during which the single dose of product or placebo is administered, a Non-Residency follow up period, and a final follow up period that is initially in residence (1 day) then non-resident (3 days).

Screening Period: Days -28 to -2 (non-resident)
Screening procedures during this period include:

- Informed consent
- Medical history
- Concomitant medications
- Physical examination
- EKG
- Vital signs
- Blood samples for hematology, clinical chemistry, coagulation parameters, and infectious disease screen
- Urine drug screen
- Alcohol and smoking intake by history
- Breath alcohol test and naloxone challenge test
- Columbia Suicidality test
- HAM-D17 test for depression
- Pregnancy test

Dosing Period: Days -1 to +3 (resident)

Subjects will become inpatients on the day prior to dosing (Day -1 and end this period of residency 72 hrs after implantation of BIOPIN 6 or placebo. On day (-1), the following will occur: medical history update, Physical examination update, concomitant medication update, suicidality repeat, depression repeat, naloxone challenge repeat, alcohol breath test repeat, urine drugs repeat, pregnancy test repeat, EKG repeat. Inclusion/exclusion criteria will be reverified.

On day 1 (0 hr), implantation of BIOPIN 6 or placebo will occur. In each of the 3 cohorts (dose-levels), subjects will be randomized 6 (BIOPIN 6) vs 2 (placebo).

Between 0 hr and 72 hr, vital signs, adverse events, and clinical chemistries will be evaluated (per study timetable). Blood for PK will be taken Predose, and at hours 1, 3, 6, 12, 24, 48 and 72.

Follow up period: Day 3 to Week 11 (non-resident)

Subjects will return for to clinic for a non-residential visit at the end of each week and also on day 10. The following will be assessed weekly: adverse events, concomitant medications. Blood will be drawn for PK weekly and also on day 10. The following will be assessed at weeks 4 and 8: physical examination, vital signs, urine drugs, suicidality, clinical chemistries, hematology, EKG. Depression will be assessed on weeks 2, 4, 6, 8, 10.

End of study: week 12 (resident, then non-resident)

Subjects will return for a residential visit on week 12 after dosing. At that time, the implant will be removed and be subject to gross and microscopic descriptions and photos of each tissue capsule. Repeat assessment will be made of adverse effects, EKG, vital signs, clinical chemistry, hematology, concomitant medications, urine drugs, suicidality/depression. To verify diminution

of naltrexone exposure post-implant-removal, blood will be taken for PK pre-explant; 1, 3, 6, 12, 24 hrs after explant (as resident); and 48, 72, and 96 hours after explant (as non-resident).

Estimated Number of Subjects to be Screened and Enrolled:

Anticipate 40-50 to be screened to enroll 24 initial subjects plus an estimated 3 replacement subjects to have 24 completers for the PK analysis. A completer is a subject with sufficient blood samples collected post dosing to make determinations of all PK parameters.

Main Criteria for Inclusion/Exclusion:

Healthy male or female volunteers, aged 18-to-55 years, with normal laboratories (chemistry, coagulation, hematology), without intake of abused drugs as verified by urine tests, without suicidality.

Investigational Product Dosage, Schedule, and Mode of Administration:

BIOPIN 6 (or matching placebo): implanted once at 4.8g, 9.6g, or 14.4g concentrations. Implantation site is a subcutaneous pocket in the upper abdominal wall.

Duration of participation:

14 weeks

Criteria for Evaluation:

PK Parameters: AUC_{∞}, AUC_t, C_{max}, t_{max}, $t_{½}$

Safety: AEs, vital signs, and clinical laboratory parameters

Statistical Methods:

Sample Size:

Six BIOPIN 6 subjects per drug level (cohort).

Pharmacokinetics:

The elimination rate constants (λ_z) will be estimated from the terminal log-linear decline in plasma concentrations and $t_{½}$ calculated as $0.693/\lambda_z$. Area under the plasma concentration curves (AUC) 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 and λ_z. The value of t_{max} will be the observed time of the highest plasma concentration and C_{max} will be the plasma concentration at that time.

Safety:

Descriptive statistics will be used to present subject baseline variables and post dosing AEs, vital signs, and clinical laboratory values.

2.2 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			
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 (see Protocol Section 8)
[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. Days 7 and 10. Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	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

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3. List of Abbreviations

ABBREVIATION TERM	DEFINITION
AE	Adverse Event
ALT	Alanine Transaminase
AR	Adverse Reaction
AST	Aspartate transferase
AUC	Area under the curve
AUC_{∞}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
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
BIOPIN 6	Bioresorbable, Polymeric Implant containing Naltrexone
BMI	Body Mass Index
C_{max}	The maximum observed plasma concentration
CAP	College of American Pathologists
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CLIA	Clinical Laboratories Improvement Act
CM	Centimeter
CRF	Case report form
CRU	Clinical Research Unit
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Terminology Criteria
CTCAE	National Cancer Institute Common Terminology of Criteria for Adverse Events
%CV	Percent coefficient of variation
DSM-IV	Diagnosis and Statistical Manual of Mental Disorders, Edition IV
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
EDMS	Electronic data management system
FDA	Food and Drug Administration

ABBREVIATION TERM	DEFINITION
FSH	Follicle-stimulating hormone
G	Gram
GCP	Good Clinical Practice
GCT	Glucose challenge test
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
KG	Kilogram
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
MedDRA	Medical Dictionary of Regulatory Activities
MG	Milligram
ML	Milliliter
mmHg	Millimeter of mercury
N	Number of Observations
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NG	Nanogram
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NOAEL	No Observed Adverse Effect Level
OTC	Over-the-counter
PK	Pharmacokinetics
PI	Principal Investigator
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell count
SAE	Serious adverse event

ABBREVIATION TERM	DEFINITION
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SQ	Subcutaneous
SD	Standard Deviation
SOP	Standard Operating Procedure
T_{max}	The observed time to reach maximum plasma concentration
$T_{1/2}$	The apparent terminal exponential half-life
UPIRTSO	Unanticipated Problem Involving Risk to Subjects or Others
WBC	White blood cell count

4. Introduction

4.1 Rationale

The opioid overdose crisis is expanding rapidly, with a staggering 70,601 deaths recorded in 2020 alone in the United States [5]. Furthermore, it is estimated that for every fatal overdose, there may be as many as seven non-fatal overdoses [7]. Opioid drugs act by binding to specific receptor sites in the brain in the ventral tegmental area and in respiratory centers. The ventral tegmental area sites are also the binding sites of endogenous opioid-like peptides that produce the feeling of being profoundly rewarded, whereas reception of opioids at the respiratory centers causes respiratory depression. Opioid withdrawal leads to the opposite of the "high" feeling when taking opioids, that is, leads to irritability, dysphoria, insomnia, anxiety, and sleep disturbances. [8; 3] Two clinical issues consequent to opioid use are therefore overdosing leading to respiratory depression and death, and also managing withdrawal in patients who attempt to do so.

Treatment of overdose is with naloxone, a rapidly acting antagonist of opioid binding at opioid receptors that is very effective if administered in time. Since however approximately 1/3 of overdoses occur in patients who have previously overdosed [6], an unmet medical need is to prevent repeat opioid use (relapse) in opioid abusers. One approach to relapse prevention is naltrexone, which like naloxone is an opioid receptor antagonist, administered intramuscularly monthly (Vivitrol). It is intended that ablation of opioid binding will prevent both the pleasure attendant to binding in the ventral tegmental area and respiratory depression attendant to binding in the respiratory control centers. Nevertheless, Vivitrol treatment has at least 3 disadvantages: 1) patients may find it difficult to accept ablation of the reward which accompanies opioid use and may not take the first dose of drug [4], 2) patients may be non-compliant with the need for repeat administration of drug each month, 3) the dose of naltrexone in Vivitrol approved in 2010 might be too low to protect opioid receptors against the larger amounts of opioids now being abused.

BIOPIN 6 contains naltrexone, and the excipients poly-d-l Lactic Acid and polycaprolactone for subcutaneous implantation. Via this formulation and its site of administration, it is intended that BIOPIN 6 can be given every 6 months, which should aid patient compliance thus anti-opioid efficacy. In addition, the BIOPIN 6 clinical development plan will examine BIOPIN 6 doses that lead to drug levels in excess of those resulting from Vivitrol administration. If these BIOPIN 6 doses are well-tolerated, the higher blood levels of naltrexone should also lead to greater anti-opioid efficacy.

The present protocol constitutes the first administration of BIOPIN 6 to humans. The primary endpoints are pharmacokinetics and safety of lower, mid, and higher BIOPIN 6 doses.

4.2 Investigational Product

The drug product, BIOPIN 6, consists of an asymmetric disc measuring 4.0 cm x 5.6 cm x 0.56 cm with all the edges rounded loaded with 4.8 grams of naltrexone contained within the excipients poly(D,L) lactide and polycaprolactone with a volume of 10 cc. Both polymers have a broad use as human materials which are well-tolerated. If a subject receives 9.6 g or 14.4 g naltrexone via BIOPIN 6, that subject receives 2 or 3, respectively, of the 10 ml implants.

4.3 Nonclinical data

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4.4 Clinical data

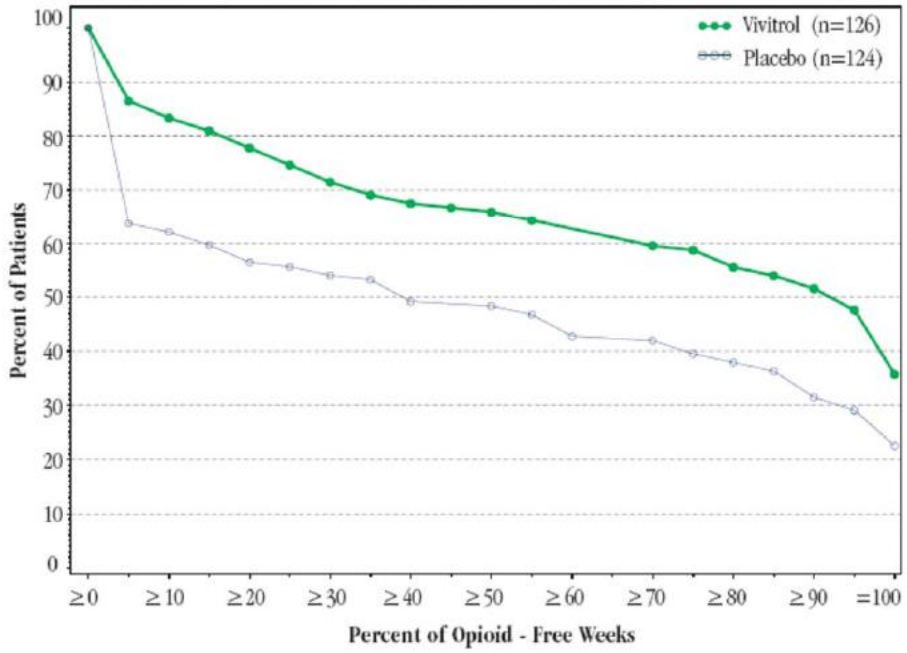
Efficacy: Although this protocol is the first administration of naltrexone in the form of BIOPIN 6 to humans, naltrexone in the form of Vivitrol has as stated above been approved for human use since 2010.

The efficacy of Vivitrol in the treatment of opioid dependence [10] was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification. Subjects were treated with an injection every 4 weeks of Vivitrol 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Standardized, manual-based psychosocial support was provided on a biweekly basis to all subjects in addition to medication.

Figure 1 below displays the cumulative percentage of subjects with opioid-free weeks ranging from no visits (0%) to all visits (100%). An opioid-free week was one in which urine drug test results were negative for opioids and self-reported opioid use was also zero. An initial period of engagement in treatment was permitted during which opiate use, if it occurred, was not considered in the analysis. Subjects discontinuing from the trial were assumed to have had opioid-use weeks for the weeks after dropout.

The cumulative percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the Vivitrol group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the Vivitrol group from Week 5 to Week 24.

Figure 1: Subjects Sustaining Varying Percentages of Opioid-Free Weeks

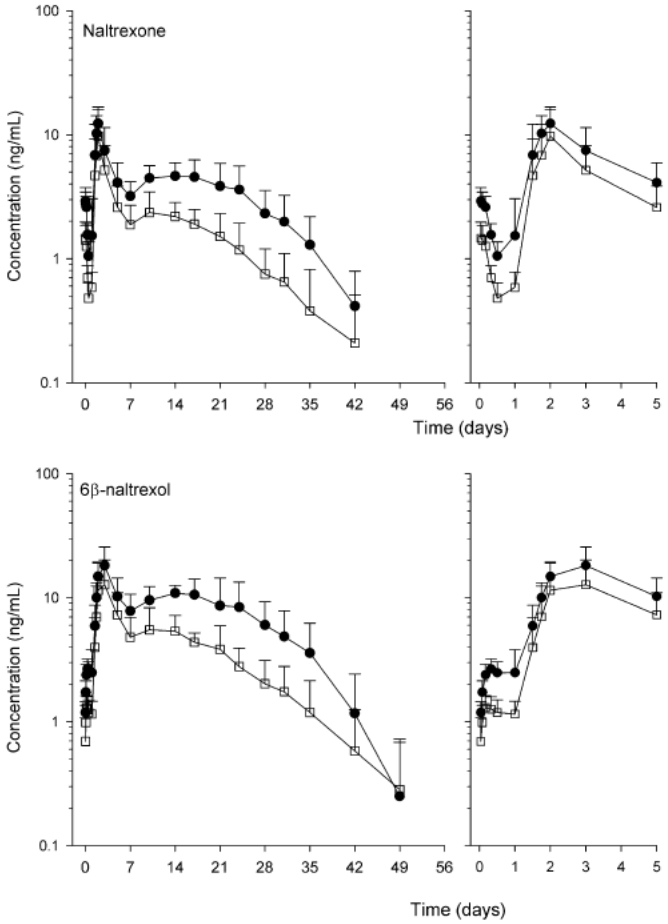


A greater percentage of subjects in the Vivitrol group remained in the study compared to the placebo group.

Pharmacokinetics: The PK of naltrexone resulting from Vivitrol administration is shown below [2]

Figure 2: Mean plasma concentration of naltrexone (top) and 6b-naltrexol (bottom) following single dose administration of long-acting naltrexone 190 (open

boxes) and 380 (closed circles) mg. Left panel: Days 0 to 56; right panel: Days 0 to 5 [2]



In this study, after naltrexone 380 mg IM, peak naltrexone levels of 10 ng/ml were achieved at day 2 and fell to 2 ng/ml on day 28. Peak 6b-naltrexole levels of 11 ng/ml on day 3 declined to 7 ng/ml on day 28.

Adverse events: The adverse events attributed to naltrexone (Vivitrol) administration for opioid dependence are: opioid withdrawal syndrome if administered to opioid-using persons, hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Additional adverse events seen in the treatment of alcohol dependences are: nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders. Suicidality has also been reported. Platelets may modestly fall; creatine phosphokinase may modestly rise. [10]

The adverse events consequent to a competitive implant containing naltrexone were: infection, irritation, side-effects of naltrexone (nausea and vomiting, weight loss or change in mood; six cases) or a requirement for opioid analgesia for co-morbid conditions (one acute trauma and one chronic rheumatological condition). [11]

The two excipients in BIOPIN 6 are polylactide and polycaprolactone, both of which are widely used clinically. Polylactide PLA has shown promise in a plethora of healthcare applications such

as tissue engineering or regenerative medicine, cardiovascular implants, dental niches, drug carriers, orthopedic interventions, cancer therapy, skin and tendon healing. It is also contained in Vivitrol. Polycaprolactone is clinically used in mesh, sutures, sinus packing, wound dressing, orthopedic implants, and dermal filler. Possible local reactions for both excipients include reactions seen with Vivitrol (pain, tenderness, induration, swelling, erythema, bruising, or pruritus; induration, cellulitis, hematoma, abscess, sterile abscess, necrosis; scarring) and those reported for polycaprolactone (pain, foreign body sensation, edema, ecchymosis, granuloma, seroma, and hematoma) [1]

The Implantation procedure may generate adverse reactions. As with any surgical procedure, implantation of BIOPIN 6 carries potential risks such as wound infection, implant extrusion, bleeding, wound dehiscence, and pneumothorax. The perioperative infection risk for pacemaker and defibrillator implantation is approximately 0.5%. Since BIOPIN 6 has no intravascular component, the infection risk should be lower.

5. Objectives and Design

5.1 Objectives

The objective of this study is to determine the pharmacokinetics and safety of single ascending doses of BIOPIN 6 in healthy volunteers.

5.2 Design

Placebo-controlled study of 3 sequential cohorts receiving 4.8, 9.6, or 14.4 g 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.

5.3 Progression to the next cohort /dose level

The progression rules are based on review of safety procedures and PK. Briefly, cohorts #2 and #3 shall be entered if the data from the preceding cohort does not show $\geq$1 grade 3-4 adverse reactions to drug , or $\geq$3 grade 2 adverse reactions to drug; and if AUC and Cmax did not exceed the values (+1 SD) seen in the preceding IND-enabling rat and dog 3-month studies.

6. Investigational Product

6.1 Investigational Product Packaging and Labeling, as below:

Protocol Number: FOR CLINICAL TRIAL USE ONLY

Subject #: ____-____ PID: #: XXXXX Retest Date: ___ ____
MMM YYYY

Contains one (1) implant of **Biopin 6 or placebo**, for subcutaneous implantation.

FOR IMPLANTATION BY TRAINED PROFESSIONAL AT THE CLINICAL SITE.

Store at 2ºC-8ºC (36ºF-46ºF). Do not open foil package until ready for use.

Caution: New Drug--Limited by United States Law to Investigational Use Only.

Sponsor: DRUG DELIVERY COMPANY, 26627 PEMBERTON DRIVE, SALISBURY, MD 21801.

6.2 Investigational Product Storage

BIOPIN 6 is contained in a sterile pouch which is stored at 4 degrees Celsius.

6.3 Investigational Product Accountability

The site principal investigator (PI) or designated study personnel will maintain a log of the receipt of all investigational products and record of dispensing of all investigational products to the subject. Investigational product for each subject will be inventoried and accounted for throughout the trial. Investigational product use during the trial will be recorded on the appropriate drug accountability form.

Unused investigational products will be retained at the clinical site until the end of the study. After final accountability has been performed, unused and explanted used investigational products will be returned to the sponsor.

6.4 Investigational Product Administration

BIOPIN 6 is a combination product consisting of naltrexone, poly-d-l Lactic Acid, and polycaprolactone to be implanted subcutaneously.

The justification for implantation, implantation procedures, and implantation risks are summarized in Appendix A.

Data concerning orientation of implants with respect to host physical sites and (for subjects receiving 2 or 3 implants) orientation of the implants with respect to each other will be recorded on case report forms.

7. Subject participation

7.1 Recruitment

Subjects will be recruited from the site's database without regard to ethnicity, race, or socioeconomic level. Standard recruiting practices such as flyers, newspaper advertisements, radio advertisements, or volunteer databases will be used to recruit study volunteers. The site's IRB will approve of all advertisements. Interested candidates between the ages of 18 and 55 years, inclusive, will be pre-screened via a telephone screening process to determine if they are in general good health and available for approximately 5 months.

7.2 Informed Consent

Subjects will be scheduled to meet with the PI or designated investigational staff and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the IRB. Subjects will be provided a copy of the signed consent form. After providing informed consent, the subject will proceed to the Screening phase of the study.

7.3 Inclusion criteria

Subjects must meet all of the following criteria to be included in the study:

1. Healthy male or female volunteer, aged 18-to-55 years, inclusive.

2. BMI must be between 18 and 32 kg/m^2 (inclusive) and weigh a minimum of 50 kg (110 lbs).

3. If female, be postmenopausal (at least 2 years prior to dosing) or agree to use an acceptable form of birth control from screening until 12 weeks after dosing. Subjects who claim postmenopausal status will have status confirmed with a follicle-stimulating hormone (FSH) test. Acceptable forms of birth control for females include the following:

- Vasectomized partner (at least 6 months prior to dosing)
- Surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to dosing
- Non-surgical permanent sterilization (eg, Essure procedure) at least 3 months prior to dosing.
- Abstinence (must agree to use a double barrier method if they become sexually active during the study)
- Double barrier (diaphragm with spermicide; condoms with spermicide; Intrauterine device with or without hormones)
- Oral hormonal contraceptives

4. Not Breast feeding

5. Negative tests for human immunodeficiency virus (HIV), Hepatitis C antibody, Hepatitis B surface antigen, and Covid antigen

6. Able and willing to comply with the requirements of the protocol

7. Able and willing to provide written informed consent

8. Willing to undergo a minor surgical procedure under anesthetic to allow for investigational drug administration in the subcutaneous tissue

9. Agree to avoid blunt trauma to the implantation site

10. Agree that after implantation, not to shower for 2 days and not to bathe/swim for 4 weeks

7.4 Exclusion criteria

Subjects must have none of the exclusion criteria to be included in the study.

1. Clinically significant abnormal finding on the physical exam, medical history, electrocardiogram (EKG), or clinical laboratory results at screening. In particular, values of liver function tests (ALT, AST, bilirubin, albumin, GGT) and kidney function tests (creatinine, blood urea nitrogen) and reticulocytes shall not deviate by more than 25% from the ranges of normal.

2. Blood pressure: systolic >150 mmHg, diastolic >90 mmHg. [Europe Soc Hypertension guidelines]. Repeat measurements up to three times are acceptable.

3. Heart rate: >100 beats/minute.

4. Hemoglobin for female <11.5 and for male <12.5 are excluded.

5. Have a known or suspected history or family history of adverse reactions or hypersensitivity to the study drugs or to drugs with a similar chemical structure.

6. History or presence of gastrointestinal, hepatic or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.

7. Is on anticoagulant medications other than aspirin or NSAIDs. Agree to stop aspirin or NSAIDs 1 week prior to Biopin 6 implantation

8. Used any over-the-counter (OTC) medication, nutritional or dietary supplements, herbal preparations, or vitamins within 7 days prior to the first dose of medication.

9. Used any prescription medication (except contraceptive medications and those required for use during the surgical procedure) within 14 days prior to the first dose of study medication.

10. More than moderate drinking averaged over the last month as assessed by history:

- Moderate drinking is here defined as up to 3 drinks per week. The standard drink will be defined by the guidelines of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and will contain no more than 14 g of alcohol.

11. Smoking: Use of tobacco or nicotine-containing products within the 3-month period preceding study drug administration is exclusionary.

12. Positive urine drug screen for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, cannabinoids, phencyclidine, propoxyphene, and methadone at the screening and Day -1 tests.

13. Any methadone use 14 days prior to screening, and up to Study Day -1.

14. Has had a naltrexone implant in the past 24 months.

15. Has received treatment with an extended naltrexone product (e.g. Vivitrol) in the past 12 months.

16. Fails the naloxone challenge test (Appendix C)

16a. Fails the alcohol breathalyzer test

17. Has a condition which requires treatment with opioid based medication.

18. Has a known hypersensitivity to naltrexone.

19 Has a known hypersensitivity to materials based on poly-d-l Lactic Acid and polycaprolactone (e.g. biodegradable sutures, surgical implants or previous biodegradable implants).

20. Has a known hypersensitivity to local anesthesia.

21. Is prone to skin rashes, irritation or has a skin condition such as recurrent eczema that is likely to impact the implant site area, or as determined by the evaluating physician.

22. Is known to form keloids at the site of skin injury.

23. Demonstrates any abnormal skin tissue in the proposed implantation area

24. Previous surgery to the upper abdominal wall

25. Donated blood or plasma within 30 days prior to the first dose of study medication.

26. Participated in another clinical trial within 30 days prior to the first dose of study medication.

27. Is participating or intending to participate in any other clinical trial during the duration of this study.

28. Any elevated risk for suicide measured using the Columbia Suicide Severity Rating Scale, endorsing any of the items in the past month (C-SSRS, Lifetime)

29. Not as much as “mild” depression as measured by the HAM-D17 test: HAM-D17 score must be 0-10.

30. Any additional condition(s) that in the investigator's opinion would prohibit the participant from completing the study or would not be in the best interest of the participant.

7.5 Duration of participation

Each subject will participate for a maximum of 5 months: up to 1 month of screening, 14 weeks of product administration and follow up.

7.6 Withdrawal criteria

Each subject may withdraw consent at any time during the study without penalty. Counseling about the subject's health will be provided if he/she decides to discontinue participation in the study. Medical advice regarding what is in the best interest of the subject will be provided.

The PI may discontinue the subject’s activity without the subject’s consent if any of these criteria is met:

- A subject fails to comply with study procedures

- A subject's safety or health may be compromised by further participation
- When premature removal of the implant is needed if pain management requires reversal of naltrexone blockade [10]

7.6.1 When and How to Withdraw Subjects

A subject may end his or her participation in the study at any time. If a subject withdraws, the investigator will make a reasonable effort to determine the reason for the withdrawal from the study and to complete termination procedures as described in section 7.6.2. Telephone calls, registered letters, and email correspondence are considered reasonable efforts for subjects who have missed clinic visits.

A subject may be withdrawn for an AE or serious adverse event (SAE) resulting in a safety concern, or for noncompliance with protocol requirements. When a subject withdraws due to an AE or is withdrawn by the PI due to an AE, the sponsor's representative must be notified within 72 hours. Investigators must follow specific policy regarding the timely reporting of AEs and SAEs to the site's IRB. In all cases, the PI will make a reasonable effort to complete study termination procedures.

7.6.2 Data Collected for Withdrawn Subjects

For subjects leaving the study before the final visit: Ongoing AEs will be followed to resolution or stabilization, if possible. All data collected up to the time of withdrawal will be reported. The subject disposition CRF will be completed, with the reason for withdrawal specified. Strenuous efforts will be made to convince the subject to return to clinic for explantation (including a final clinical chemistry and hematology panel) and for clinical follow-up 2 weeks after explantation. If the subject refuses explantation, documented attempts will be made to contact the subject for AE checks until 9 months after implantation.

7.6.3 Replacement of Subjects

Enrollment will continue until 8 subjects in each group meet the criteria for a study completer. A completed subject is one who provides blood samples through Week 12 that is sufficient for PK parameters to be determined. A "PK completer" is defined as a subject with a maximum of 2 missed PK samples through 24 hrs, a maximum of 1 missed sample from 24 hrs through day 10, and a maximum of 2 missed samples for the 2 week-through- preexplant week 12 time period. If a subject is withdrawn, the replacement subject will be assigned to the same treatment group (BIOPIN implant, placebo implant) as the withdrawn subject.

7.7 Entrance of subjects into a cohort

To verify that a new dose level is initially well-tolerated, approximately half that cohort will complete the 72-hr residential phase surrounding device implantation before the rest of that cohort will have device implantation. In practice, this means that about 4 of the 8 subjects in each cohort will be entered in each of 2 weeks.

7.8 Progression of cohorts

7.8.1 Safety considerations: Progression of dose levels (entrance of a new cohort at the next higher dose level) will depend on review of the safety data **at least through week 4** of the prior dose level.

The primary basis on which drug escalation would be limited is based on adverse reactions (an adverse event at least possibly attributable to drug). The committee that evaluates the adverse events for their relationship to drug and implements the progression rules will consist of the PI and a representative of the Sponsor, with the assistance of the Clinical Monitor and the study statistician. Before the blind is broken, the Committee will determine the grade of an AE and whether the AE is not-likely/unlikely related to implantation (ie, there is likely an alternate etiology for the event).

Progression procedures and rules:

SARs: If 1 subject at a dose level experiences an SAE that is decided after breaking the code to be an SAR, further entry into that dose level will be at least temporarily stopped. Further accrual to that dose level may carefully proceed with more frequent adverse event monitoring and reporting. The timing of additional AE monitoring will depend on the time the SAR occurred. The additional event data, whether adverse or not, will be reported and considered by the PI and representative of the Sponsor within 7 days, with an SAE reported within 3 days. If a 2nd subject experiences an SAR, accrual to that dose level will stop and accrual to the study will stop. If not more than 1 of the 6 Biopin subjects at that dose-level experience an SAR, 8 further subjects (randomized 6 Biopin vs 2 placebo) will be entered into that dose level. Progression to the next dose-level will occur if none of the extra 6 Biopin subjects experience an SAR or a grade 4 AR.

Grade 3-4 Adverse Reactions: If ≥ 1 of the 6 BIOTIN 6 subjects at a dose level experiences a grade 3-4 adverse event evaluated in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (Ver 5.0) that is decided after breaking the code to be an adverse reaction, escalation to the next level of drug will be at least temporarily stopped. Progression to the next dose level will not occur unless 8 more subjects (randomized 6 Biopin vs 2 placebo) have been entered into the present dose level without any grade 3-4 adverse reactions.

Grade 2 Adverse Reactions: If ≥ 3 of the 6 BIOPIN 6 subjects at a dose level experience a grade 2 adverse event determined after breaking the code to be an adverse reaction, escalation to the next level of drug will be at least temporarily stopped. Progression to the next dose level will not occur unless more subjects have been entered into the present dose level with no more than one grade 2 adverse reactions.

If 0-2 of the subjects at a dose level experiences a grade 2 adverse event, escalation to the next dose level will proceed.

7.8.2 Pharmacokinetic considerations

Progression of dose levels (entrance of a new cohort at the next higher dose level) will also depend on review of the naltrexone PK data of the prior dose level. AUC (0-T) will be calculated for T=4 weeks, T= 8 weeks, and T=12 weeks for each subject, statistically summarized for the group, and the mean values will be compared to the reference values for the most sensitive animal species (dog) for which AUC was 3,267 ng/ml x hr up to 4 weeks, 6,117 ng/ml x hr up to

8 weeks, and 13.239 ng/ml x hr up to 12 weeks. In addition, the mean Cmax for dog for which the reference value was 42 ng/ml. If the mean clinical Biopin AUC or Cmax values exceed any of these reference values by 31%, the new cohort will not be entered until further consultation with the FDA.

7.9 Termination of the Study

If, in the opinion of the investigator, the clinical observations in the study suggest that it may be unwise to continue, the investigator may terminate the study after consultation with the Study sponsor. A written statement fully documenting the reasons for such a termination will be provided to the sponsor. In addition, the sponsor may terminate the study at any time. Furthermore, if it becomes apparent that subject enrollment is unsatisfactory with respect to quality or quantity or that data recording is inaccurate or incomplete on a chronic basis, the sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the investigator, the IRB/IEC, and regulatory authorities, if required. In the event any serious adverse events (SAEs) are part of the reason for early termination of the study, all documentation relating to the event(s) reported to FDA must be obtained and filed appropriately.

8. Procedures

8.1 Screening: days -28 to -2

Demographics: Demographics data include the subject's age, gender, and race/ethnicity.

Medical history: A medical history will be taken during screening for all potential study subjects to assure medical fitness. Drug allergies will be queried. Drinking and smoking habits will be queried

Physical examination: A physical examination of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen, extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening. Weight (kg) and height (centimeters) will be collected.

EKG: A 12-lead resting EKG will be obtained.

Vital signs: Vital signs to be assessed include sitting blood pressure and pulse rate (after sitting for at least 3 minutes). Site is allowed to repeat Screening vital signs up to 3 times towards inclusion in the trial.

Clinical pathology: Clinical laboratory tests will be performed at the clinical site's local clinical laboratory. The laboratories performing these assessments should be directly regulated by the College of American Pathologists (CAP) or Clinical Laboratory Improvement Act (CLIA) guidelines. The laboratory will need to provide a copy of current certification. The following tests will be performed to determine the medical fitness of the subject for participation:

Clinical Chemistry: ALT, Albumin, alkaline phosphatase, AST, bilirubin (total and direct), calcium, chloride, cholesterol, creatinine, GGT, glucose, phosphate, potassium, sodium, total protein, BUN, uric acid.

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

Coagulation: Fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT).

Infectious Diseases: Hepatitis B surface antigen, Hepatitis C antibody, Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen, Covid antigen.

Pregnancy tests: A serum test for β-hCG will be performed. Serum HCG test at screening; urine HCG test at day (-1). For postmenopausal females, a follicle stimulating hormone test will be performed during screening.

Urine drug tests: Urine drug tests will be used to assess candidates for recent use of amphetamines, barbiturates, benzodiazepines, cocaine, opiates, cannabinoids, phencyclidine, propoxyphene, and methadone.

Alcohol breathalyzer test: An alcohol breathalyzer test measures the amount of alcohol in the blood. The subject must have a blood alcohol levels of $\leq$0.05% to be enrolled in this study.

Naloxone challenge test: The naloxone challenge test is performed to assess physical dependence. 0.1 mg of naloxone is administered subcutaneously . A positive test is indicative of physical dependence and consists of typical withdrawal symptoms and signs. These symptoms and signs usually last for 30-60 minutes. The test will be administered as per SOP (Appendix C).

Suicidality: Suicidality will be measured by Columbia Suicide Severity Rating Scale. Data will be collected for both “Lifetime” as well as “Past 1 month”.

Depression: Depression will be measured by the HAM-D17.

Inclusion/exclusion criteria: Verified.

8.2 Day (-1) to day 3 (72 hr after dosing)

Subjects will become in residence on day -1 and end this period of residency 72 hrs after implantation of BIOPIN 6 or placebo.

On day (-1), the following will occur: medical history update, Physical examination update, concomitant medication update, suicidality repeat, depression repeat, naloxone challenge repeat, , urine drugs repeat, pregnancy urine repeat. EKG repeat. Inclusion/exclusion criteria will be reverified.

On day 1 (0 hr—defined as the beginning of implantation), implantation of BIOPIN 6 or placebo will occur via Appendix A. The measures used to prevent complications of implantation are given at the end of Appendix A.

In addition to the implant parameters required by Appendix A, the following assessments will be performed after implantation:

-distance (cm) to the incision of the closest palpable edge of the implant,

-photo of the implant site [outline each palpable implant with a blue marker on subject’s skin, metric ruler in photo]

Between 0 hr and 72 hr, vital signs, adverse events, and clinical chemistries and hematology will be evaluated (per study timetable). Blood for PK will be taken Predose and at hours 1, 3, 6, 12, 24, 48 and 72. Acceptable time windows will be +/- 1 hr up to 24 hrs and +/-3 hrs for the 48 and 72 hr draws.

8.3 Weeks 1-to-11 after dosing

Subjects will return for to clinic for a non-residential visit on day 10 and at the end of each week. The following will be assessed weekly: adverse events, concomitant medications. Blood will be drawn for PK on days 7 and 10 and then weekly. Vital signs will be assessed on Days 7 and 10, and on Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 The following will be assessed at weeks 4 and 8: physical examination, urine drugs, suicidality, depression, clinical chemistries, hematology, EKG, implant assessment (distance from incision, photo of site) as per after-implantation. For these non-residential visits, acceptable time windows will be the target day +/- 3 days.

The implant parameters required by Appendix A will be assessed at each residential and non-residential visit, or if the subject brings it to the attention of the study team. The measures used to prevent complications if they occur are given at the end of Appendix A.

8.4 Week 12 and 14: study end

Subjects will return for a residential visit on week 12 after dosing. Prior to removal, the implant **parameters required by Appendix A** will be assessed (distance from incision, photo of site) as

per after-implantation. At that time, the implant will be removed (Appendix B) and be subject to Gross and microscopic descriptions and photos of each tissue capsule. Blood will be taken for PK pre-explant and 1, 3, 6, 12, 24, 48, 72, 96 hrs after explant. Sampling up to 24 hrs will be as residents; sampling at 48, 72, and 96 hrs (+/- 4 hrs) will be as non-residents. Repeat assessment will be made of adverse effects, vital signs, clinical chemistry, hematology, EKG, concomitant medications, urine drugs, suicidality, depression.

On week 14, 2 weeks after implant removal, the subjects will return for a non-residential visit for surgical evaluation of the implant removal site.

8.5 Concomitant medications

Subjects must abstain from taking any prescribed medications within two weeks prior to dosing and over-the-counter remedies within 7 days prior to dosing until completion of the study. Any medications taken in the 30-day period prior to the start of screening will be recorded as prior medications. However, certain medications for symptomatic relief can be taken with the prior knowledge and approval of the investigator.

9. Endpoint Assessment and Analysis

9.1 PK

Sample collection and analysis: Blood will be collected in 4 mL K_2EDTA Vacutainer tubes to obtain plasma for PK determination at the 29 times specified in the protocol timetable. The time of blood collection will be recorded. Blood samples will be placed on ice immediately after collection and then centrifuged to separate plasma within 30 minutes of collection. Approximately 1 mL of plasma will be aliquoted into the primary vial and the remaining volume of plasma will be aliquoted into a back-up tube. The primary and back-up tubes are to be stored at -60°C to -80°C until analysis.

Plasma samples for naltrexone and 6b-naltrexole determination will be analyzed using a validated LC/MS/MS method. A method validation report will be issued for the validated method and a bioanalytical report for the sample analysis.

PK analysis: The concentration-time profiles will be evaluated by non-compartmental analysis. Actual sample times will be utilized for calculations. Calculations of parameters will be performed with Phoenix WinNonLin 6.2 (Pharsight Corporation, St. Louis, MO). 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.

The following definitions apply to PK parameters:

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 $\ln(2)/\lambda_z$.

Mean, SD, geometric mean, median, minimum and maximum plasma concentrations will be presented for each PK parameter.

9.2 Safety

Adverse Events and Serious Adverse Events**:** AE data will be listed individually and summarized by Medical Dictionary for Regulatory Activities (MedDRA) body system and preferred terms within a body system by severity and relationship to the investigational product. Serious and/or unexpected AEs will also be discussed on a case-by-case basis. For the tabulation of the AEs by

preferred term, a subject will be counted only once under each preferred term by maximum severity and closest relationship to the investigational product.

Clinical Laboratory Data (chemistry, hematology, coagulation, infectious serology, urine drugs): The mean, SD, mean change where applicable, median, and range of all values for each test at each time point will be presented in a summary table. Values will be compared to normal according to CTC v 5.0. Individual abnormal values will be presented and discussed.

Vital signs including blood pressure and heart rate will be presented as summary statistics and change from baseline. Values will be compared to normal according to CTC v 5.0. Individual abnormal values will be presented and discussed.

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

Suicidality and depression: For the Columbia Suicide Severity Rating Scale, the number and percentage of subjects that endorse suicidal ideation and suicide attempt will be presented. For HAM-D17 scores , the mean, SD, change from screening, median, and range of all values at each time point will be presented in a summary table. Scores of 0 to 7 are considered to not be indicative of clinical depression.

Demographics and other entrance examinations: Summaries of the subject demographics, blood alcohol tests, and naloxone challenge tests will be presented.

By-subject listings will be provided for clinical laboratory, vital signs, demographic data, medical history, physical examination results, vital signs, blood alcohol tests, naloxone challenge tests, concomitant medications, depression/suicidality.

9.3 General Statistical methods

9.4 Sample size

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

9.5 Statistical reporting

Detailed statistical procedures, listings, table shells and figures will be provided in a separate statistical analysis plan (SAP) written shortly after protocol approval but before any subject enrollment. The SAP will be finalized before study close-out and database lock. The following key statistical components will be considered and a detailed description will be documented in the SAP:

- Primary and secondary endpoints and how they will be measured,
- Statistical methods that will be used to analyze the endpoints,
- Strategy that will be used if the statistical test assumptions are not satisfied,

9.5.1 Description of statistical methods

Descriptive statistics will be used to present study data. Continuous variables will be presented as number of observations (n), mean, standard deviation (SD), geometric mean (for drug plasma concentrations) percent coefficient of variation (%CV) (of plasma concentrations), median,

minimum and maximum values. Categorical variables will be presented as counts and percentages.

9.5.2 Accounting for Missing, Unused, and Spurious Data

Missing safety data (laboratory or vital sign values) will be ignored and numbers of values reported will be presented in tables. If a subject missed too many blood samples to determine the PK profile, then the subject will be excluded entirely from the PK analysis.

9.5.3 Procedures for Reporting Deviations from the Original Statistical Plan

Any deviation(s) from the original SAP will be documented in the clinical study report.

9.5.4 Selection of Subjects to be Included in Analyses

All dosed subjects will be included in the presentation of safety data. Only those subjects who provide sufficient data to determine PK parameters will be included in the PK analysis.

10. IND Safety Reporting

The following terms, as defined by 21 CFR 312.32, apply to IND safety reporting.

10.1 AE or suspected AR

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

10.2 SAE or serious suspected AR

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.3 Unanticipated AE or unexpected suspected AR

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AE or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.4 Unanticipated problems involving risks to subjects

Federal regulations require that unanticipated problems involving risks to subjects or others (UPIRTSO) be promptly reported to the IRB. These events encompass a broader category of events than SAEs and may include issues such as problems with loss of control of subject data or the investigational product; adverse psychological reactions; or breach of confidentiality. Risks to others (eg, program personnel) must also be reported.

Unanticipated problems involving risks to subjects or others are any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the procedures that are described in the protocol, investigators brochure or informed consent document; and (b) the characteristics of the subject population;
- Related or possibly related to a subject's participation in the study; and
- Suggests that the study places subjects or others at a greater risk of harm than was previously known or recognized.

The IRB will evaluate the PI's and medical monitor's reports to determine whether a given incident, experience or outcome constitutes an unanticipated problem involving risk to subjects or others and, in coordination with the sponsor, ensure upward reporting of the unanticipated problems involving risk to subjects or others to the appropriate regulatory offices.

10.5 Relationship to investigational product

The investigator must assign a relationship of each AE to the receipt of the investigational product. The investigator will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. The following guidelines should be used by investigators to assess the relationship of an AE to study product administration. A physician and/or licensed practitioner (eg. NP, PA) are able to make this determination.

Not related: No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.

Unlikely related: Likely unrelated to the investigational product. Likely to be related to factors other than investigational product, but cannot be ruled out with certainty.

Possibly related: An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the subject's clinical status or underlying factors including other therapy.

Related: An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

10.6 Severity Assessment

All AEs will be assessed for severity by the investigator. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. Each event will be assigned one of the following categories: mild, moderate, severe, or life-threatening. Clinically Significant labs should be reported as AEs. Abnormalities in vital signs will be reviewed by the Investigator staff. The Investigator will have the authority to determine if any action needs to be taken with the abnormal vital signs and/or if the abnormality should be considered an AE. All laboratory abnormalities and vital sign abnormalities graded in accordance with CTC AE criteria will be considered when implementing progression rules (Section 7.8.1).

Any grade 4 (life-threatening) AE must be reported as an SAE.

The eCRF for AEs will reflect only the highest severity for continuous days an event occurred.

Mild	Grade 1	Does not interfere with routine activities Minimal level of discomfort
Moderate	Grade 2	Interferes with routine activities Moderate level of discomfort
Severe	Grade 3	Unable to perform routine activities Significant level of discomfort
Potentially life-threatening	Grade 4	Hospitalization or ER visit for potentially life-threatening event

FDA guidelines for toxicity will be followed; however, if a subject is evaluated in an emergency room for nonlife threatening illness or symptoms (ie, visits emergency department on weekend for mild problems because the physician's office is closed), the information from that visit will be reviewed and severity of the adverse event will be assessed according to the subject's clinical signs and symptoms.

As defined by the ICH guideline for GCP, the term "severe" is often used to describe intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.7 Recording AE

Methods/Timing for Assessing, Recording, and Analyzing Safety Endpoints:

AEs and SAEs will be assessed in accordance with the schedule in the protocol timetable in Section 2.2 documented in the source records, and recorded on the eCRFs using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess all AEs for seriousness, relationship to investigational product, severity, and other possible etiologies. When an event has not resolved when the subject completes the study, it will be documented on the AE eCRF as "ongoing".

Duration of Follow-Up of Subjects after Adverse Events:

Investigators are required to follow SAEs to resolution, even if this extends beyond the prescribed reporting period. Resolution is the return to baseline status or stabilization of the condition with the probability that it will become chronic. The SAE outcomes will be reported to the sponsor's representative using the SAE eCRF.

10.8 Reporting AE

The PI will report all AEs to the site's IRB in the appropriate safety, annual, and/or final reports.

10.8.1 Reporting Serious and Unexpected Adverse Events

Contact information for reporting SAEs is provided in Table 1.

10.8.2 Reporting to the Sponsor

All SAEs and other relevant AEs must be reported promptly (within 24 hours) to the sponsor's representative as per 21 CFR 312.64, whether or not the event is considered related to study product. Notifications will be provided to the persons/entities listed in Table 1. Further, the investigator should comply with relevant study site SOPs on reporting SAEs to the site's IRB.

The minimum information that the investigator will provide is specified in Table 2. The sponsor's representative may request additional information for purposes of the study.

Table 1: Study Contacts for Reporting Serious Adverse Events and Unanticipated Problems Involving Risks to Patients or Others

Sponsor's Representative (All SAE and Unanticipated Problems)	Lawrence Blob, MD Cognitive Research Corporation 200 Central Avenue, Suite 1200, St. Petersburg, FL 33701 410-262-1908 lblob@cogres.com Safety@cogres.com

Table 2: SAE Information to be Reported

Notification Method	Information to be Provided
Email or Telephone (within 72 hours)	IND number, sponsor study number, name of the investigational product, and investigator name and contact number
	Subject identification number
	SAE name and description, onset date, date of investigational product administration, severity, relationship to the investigational product, and subject's current status
AND	
Email or Fax	Cover sheet or letter
	Adverse event eCRF
	Serious adverse eCRF
	Concomitant medication eCRF
	Medical record progress notes including pertinent laboratory/diagnostic test results

In order to comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 calendar days, investigators must submit additional information as soon as it is available. The sponsor's representative will report unexpected SAEs associated with the use of the drug to the FDA as specified at 21 CFR 312.32 (c).

Investigators must follow all relevant regulatory requirements as well as specific policy regarding the timely reporting of SAEs to the sponsor's representative, the site's IRB.

10.8.3 Reporting to the Site's IRB

Unanticipated problems involving risk to subjects or others, SAEs related to participation in the study, and all subject deaths related to participation in the study should be promptly reported by telephone, email, or fax to the site's IRB. A complete written report should follow the initial notification.

Investigators are required to forward safety information provided by the sponsor's representative to the IRB.

10.8.4 Reporting Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

UPIRTSO are to be reported to the site's local IRB within 72 hours of learning of the UPIRTSO. Include the IND number, sponsor study number, name of the investigational product, and investigator name and contact number along with a description of UPIRTSO.

10.8.5 Pregnancy

Each pregnancy must be reported *immediately* (within 24 hours of identification) by email to the sponsor's representative. Report the incident to site's IRB in accordance with IRB policy.

Subjects who become pregnant after Day 1 will be followed to term, and the following information will be gathered for outcome: date of delivery, health status of the mother and child including the child's gender, height and weight. Complications and or abnormalities should be reported including any premature terminations. A pregnancy is reported as an AE or SAE only when there is suspicion that the investigational product may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy including a spontaneous abortion or an elective termination for medical rationale.

10.8.6 AE-related Withdrawal of Consent

Any AE-related withdrawal of consent during the study must be reported *immediately* (within 24 hours of identification) by email to the sponsor's representative. Report the withdrawal to site's IRB in accordance with IRB policy.

10.8.7 Pending Inspections/Issuance of Reports

The knowledge of any pending compliance inspection/visit by the FDA, Office for Human Research Protections (Department of Health and Human Services), or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the site's IRB and the sponsor's representative.

10.9 Other reports

Final Report: A final study report will be prepared in accordance with "Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" and ICH E3 Guideline "Structure and Content of Clinical Study Reports" and provided to the sponsor's representative for review and approval. The sponsor's representative will use this report to prepare the final clinical study report for submission to the FDA.

11. Monitoring

Direct Access to Source Data/Documents

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject. Representatives of the sponsor's representative, the site's IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied medical and research records.

11.1 Study Monitoring

Study monitoring will be the responsibility of Cognitive Research Corporation. Upon successful approval of the protocol and establishment of the regulatory file, the clinical monitor will establish a clinical monitoring plan. To ensure that the investigator and the study staff understand and accept their defined responsibilities, the clinical monitor will maintain regular correspondence with the site and may be present during the course of the study to verify the acceptability of the facilities, compliance with the investigational plan and relevant regulations, and the maintenance of complete records. As needed, the clinical monitor may witness the informed consent process or other applicable study procedures to assure the safety of subjects and the investigators' compliance with the protocol and GCPs.

Monitoring visits by a sponsor's representative-designated clinical monitor will be scheduled to take place at the initiation of the study, during the study at appropriate intervals, and after the last subject has completed the study. A report of monitoring observations will be provided to the PI and the sponsor's representative.

11.2 Audits and Inspections

Authorized representatives of the sponsor, the FDA, the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guideline of the ICH, and any applicable regulatory requirements.

11.3 Institutional Review Board

The study is based on adequately performed laboratory and animal experimentation and will be conducted under a protocol reviewed by the site's IRB. The study is to be conducted by scientifically and medically qualified persons. The IRB will determine whether the benefits of the study are in proportion to the risks. The rights and welfare of the subjects will be respected; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 CFR Part 50 and the Belmont Principles.

Enrollment in this protocol may not begin until all approvals have been obtained and the formal authorization letter is received by the PI from the sponsor's representative.

As the IRB of record, Advarra will serve as the responsible IRB and will review the protocol, informed consent, and progress reports on a continuing basis in accordance with all applicable regulations, including Title 21, Code of Federal Regulations (CFR), Parts 50 and 56.

The PI must obtain IRB approval for the study. Initial IRB approval and all materials approved by the IRB for this protocol, including the patient consent form and recruitment materials, must be maintained by the protocol physician and made available for inspection.

11.4 Quality Control and Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor's representative may conduct quality assurance audits.

Auditing of the clinical trial may be conducted at any time during the study to ensure continued compliance with regulations, policies and procedures. Auditing will be undertaken, as needed, by independent personnel designated by sponsor's representative. Audit findings will be documented in a formal audit report that will detail the conduct of the audit and summarize the observations noted.

11.5 Protocol Modifications

All modifications to the protocol and supporting documents (informed consent, study-specific procedures, SOPs, recruitment materials, etc) must be reviewed and approved prior to implementation. Any protocol amendment will be agreed upon and approved by the sponsor's representative prior to submission to the site's IRB prior to implementation of said change or modification. Any modification that could potentially increase risk to subjects must be submitted to the FDA prior to implementation. The informed consent document must be revised to concur with any amendment as appropriate and must be reviewed and approved with the amendment. Any subject already enrolled in the program will be informed about the revision and asked to sign the revised informed consent document if the modification directly affects the individual's participation in the program. A copy of the revised, signed, and dated informed consent document will be given to the subject. All original versions of the informed consent document will be retained in the protocol regulatory file, and a copy will be retained in the protocol regulatory file.

11.6 Protocol deviations

All subject-specific deviations from the protocol (eg, failure to return for follow-up visits or blood collection within the time indicated in the protocol) are to be documented. The PI or designee will be responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study specific procedure. Significant deviations will be reported annually in the continuing review report to the site's IRB and, if appropriate, in the final study report. Action taken in response to the deviation will also be recorded and entered into an eCRF.

Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study, the deviation will be reported immediately to the sponsor's representative, site's IRB.

12. Ethics

12.1 HIPAA

HIPAA requires that researchers obtain the subject's permission (HIPAA Authorization) to use and disclose health information about the subject that is either created by or used in connection with this research. The information includes the entire research record and supporting information from the subject's medical records, results of laboratory tests, and both clinical and research observations made during the individual's participation in the research.

In this research, the subject's health information will be collected and used to conduct the study; to monitor the subject's health status; to measure effects of the investigational product; to determine research results, and possibly to develop new tests or procedures. Health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. After the study ends, each subject has the right to see and receive a copy of his/her information.

Representatives of the IND sponsor, the site's IRB, and the FDA are eligible to photocopy and review records related to this protocol as a part of their responsibility to protect the participants of this protocol. In addition, these representatives are eligible to witness the applicable study procedures to assure the safety of subjects.

No personal identifier will be used in any publication or communication used to support this research study. The subject's identification number will be used in the event it becomes necessary to identify data specific to a single subject.

12.2 Compensation for Participation

The standard compensation policy for Phase 1 subjects at JBR Clinical Research will be followed.

12.3 Written Informed Consent

The informed consent process and document will be reviewed and approved by the site's IRB and the sponsor's representative prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR 50. The consent document indicates that by signature, the subject, permits witnessing of applicable study procedures by the sponsor's representative, as well as access to relevant research records by the sponsor's representative and by representatives of the FDA. The sponsor's representative will submit a copy of the initial IRB and sponsor's representative approved consent form to the FDA and will maintain copies of revised consent documents that have been reviewed and approved by the site's IRB.

A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for that subject. This consent document must be retained by the investigator as part of the study records. Each subject will receive a copy of the signed informed consent document. The investigators or their designees will present the protocol in lay terms to individual subjects. Questions on the purpose of the protocol, protocol procedures, and risks to the subjects will then be solicited. Any question that cannot be answered will be referred

to the PI. No subject should grant consent until questions have been answered to his/her satisfaction. The subject should understand that the study product is an investigational drug and is not licensed by the FDA for commercial use, but is permitted to be used in this clinical research. Informed consent includes the principle that it is critical the subject be informed about the principal potential risks and benefits. This information will allow the subject to make a personal risk versus benefit decision and understand the following:

- Participation is entirely voluntary,
- Subjects may withdraw from participation at any time,
- Refusal to participate involves no penalty, and
- The individual is free to ask any questions that will allow him/her to understand the nature of the protocol.

Should the protocol be modified, the subject consent document must be revised to reflect the changes to the protocol. If a previously enrolled subject is directly affected by the change, the subject will receive a copy of the revised informed consent document. The approved revision will be read, signed, and dated by the subject.

13. Data handling and record keeping

The primary source document for this study will be the subject's research record. The source documents will be retained at the site.

For this study, an electronic data management system (EDMS) will be used for the collection of the study data in an electronic format. The EDMS will be designed based on the protocol requirements, the approved eCRF layouts and specifications, and in accordance with 21 CFR Part 11. The eCRF layouts and specifications define and identify the applicable source data that will be collected and captured into the EDMS. The applicable source data will be electronically transcribed by the site designee onto the eCRF (data entry screens) in the EDMS. The investigator is ultimately responsible for the accuracy of the data entered into eCRFs. Data monitoring and management will be performed in the EDMS by the study clinical monitor and the designated Data Management Center.

A detailed data management plan will be written by the Data Management Center and approved by the sponsor’s representative prior to study start. All updates to the data management plan must be approved before study close-out and database lock.

13.1 Inspection of Records

The sponsor’s representative or designee will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject’s source documents, and other records relative to study conduct.

Subjects’ health information is used to report results of research to the sponsor’s representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. The consent document indicates that by signature, the subject permits access to relevant medical records by the sponsor’s representative and by representatives of the FDA.

Upon a subject’s termination from the trial, completed eCRFs will be ready and available for on-site review by the sponsor’s representative or the designated representative within 14 days after collection of the subject’s data.

13.2 Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved for 2 years following the discontinuance of the investigational product for investigation. If it becomes necessary for the sponsor’s representative or designee or the FDA to review any documentation relating to the study, the investigator must permit access to such records.

Completed, monitored eCRFs will be stored in a secure location by the sponsor’s representative or designee. The Data Management Center will provide electronic records for completed eCRFs to be retained by the investigator.

The PI will be responsible for retaining sufficient information about each subject, i.e., name, address, telephone number, Social Security number, and subject identifier in the study, so that the sponsor’s representative, the site’s IRB, the FDA, or other regulatory authorities may have access to this information should the need arise.

14. References

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Appendix A: Surgical Implantation Technique for the BIOPIN Implant: Instructions for Use

REDACTED

Appendix B: Surgical Removal Technique for the BIOPIN Implant

REDACTED

Appendix C: Naloxone Challenge Test

The subject will be administered a 0.1 mg dose of naloxone SC. Prior to administration and after naloxone administration subjects will be monitored for vital signs (heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature) pupil diameter, and other signs (sneezing/coughing, yawning, lacrimation, rhinorrhea, shivering, restlessness, sweating, vomiting, gooseflesh, and pupil size).

Failure criteria—Physiologic measures: increases in heart rate, systolic blood pressure, diastolic blood pressure, or respiratory rate by **25**%; increase in temperature by 1 degree Fahrenheit.

Failure criteria---other measures (table 5a): grade 3 or 4 responses on any parameter

If the cardiovascular measures do not return to the baseline pretreatment values (± 10%) by 30 minutes after naloxone administration, cardiovascular monitoring will continue until those indices return to the range of values (± 10%) measured during the pre-treatment observation period.

Table 3: Assessments Performed During the Naloxone Challenge Session[a]

Assessments	**Relative Time in Minutes**				
	-30	**-15**	**0**	**15**	**30**
Naloxone Administration[b]			X		
Vital Signs[c]	X	X		X	X
Other signs including Pupil Diameter (Table 5a)		X		X	X

[a] Assessments are performed in the order listed in the table from top to bottom.

[b]Naloxone 0.1 mg SC

[c] Vital signs include heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, skin temperature.

Table 5a: Scoring Guide for objective signs on Naloxone challenge test [12]

Objective sign	*Score*			
	None (code 1)	*Mild (code 2)*	*Moderate (code 3)*	*Severe (code 4)*
Sneezes, coughs	0	1-2	3-10	>10; uncontrollable bouts
Yawns	0	1-2	3-10	>10; uncontrollable bouts
Lacrimation	0	Barely noticeable watering of eyes; some blinking	Tearing, blinking, rubbing at eyes, occasional tears from corners of eyes	Profuse weeping, tears running down face, wiping eyes with handkerchief
Rhinorrhea	0	Barely noticeable sniffing	Visible nasal secretion, swallowing postnasal drip, wiping nose with handkerchief	Profuse secretion running from nose, continual use of handkerchief
Shivering	0	Barely noticeable shivering, localized, transient	Bouts of shivering involving whole body, no teeth chatter	Continuous uncontrollable shivering, teeth chattering
Restlessness	0	Greater than normal movement of limbs or body	Repeated movements of extremities, shifting of body position	Continual movement, unable to sit still, walking around, tics, chain smoking, etc.
Sweating	0	Barely noticeable moistness of palms, forehead, armpits	Readily visible wetness of skin, palms, armpits	Sweat dripping from forehead, armpits, chest
Vomiting	0	Retching, spitting up gastric contents	1-2 productions of vomitus	>2; uncontrollable vomiting
Gooseflesh (upper arms and thorax only, not periareolar)	0	Transient or intermittent gooseflesh of upper arms and/or thorax; feels smooth on palpation	Gooseflesh persisting over 30 sec; barely palpable	Gooseflesh over most of body; persisting over 60 sec; readily palpable
Mydriasis	0	Estimated pupil diameter increases 1-2 mm	3-4 mm	>4 mm