A PILOT PHARMACOKINETIC TRIAL OF THE O'NEIL LONG ACTING NALTREXONE IMPLANT

Protocol Identifying Number: GM0017

Principal Investigator: Dr. Adam Bisaga

Sponsor: Go Medical Industries Pty Ltd

Funded by: NIDA 1UG3DA047720-01

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11 June 2020

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II. INDEX OF TABLES AND FIGURES

III. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term or Abbreviation	Description
6βN	6-β-naltrexol
ADR	Adverse Drug Reaction
AE	Adverse Event
AMPRF	Australian Medical Procedures Research Foundation
AUC	Area Under the Curve
BDI	Beck Depression Inventory-II
CMP	Clinical Monitoring Plan
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CRO	Contract Research Organization
CUMC	Columbia University Medical Center
DSMB	Data Safety Monitoring Board
ECG	Electrocardiography
eCRF	Electronic Case Report Forms
EUC	Electrolytes, Urea, Creatinine
FBC	Full Blood Count
FCP	Full Chemistry Panel
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
LFT	Liver Function Tests
MEC	Minimum Effective Concentration
MSDS	Material Safety Data Sheet
NCT	Naloxone Challenge Test
NTX	Naltrexone
NYSPI	New York State Psychiatric Institute
OLANI	O'Neil Long Acting Naltrexone Implant
PHQ	Patient Health Questionaire
PI	Principal Investigator
QC	Quality Control

Term or Abbreviation	Description
UA	Urinalysis
UDS	Urine Drug Screen
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SLV	Since Last Visit
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SURC	Substance Use Research Center

IV. STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the New York State Psychiatric Institute Institutional Review Board except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Adam Bisaga M.D.

Signed: 

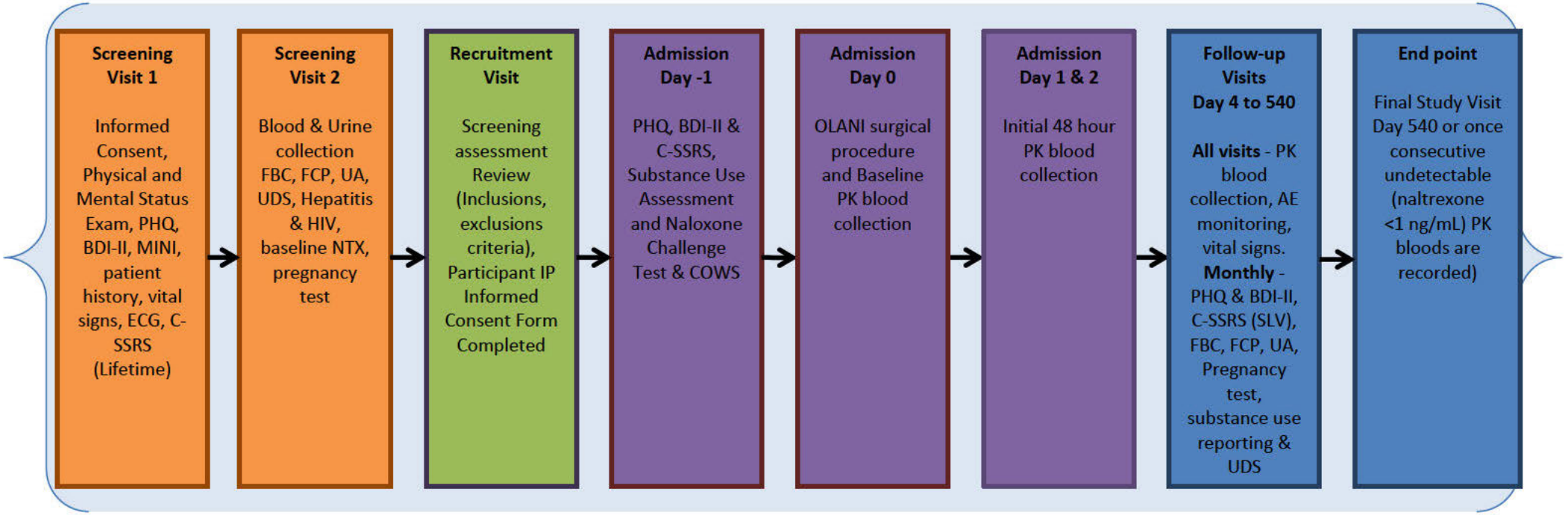
Date: June 11, 2020

V. PROTOCOL SUMMARY

Title:	**A PILOT PHARMACOKINETIC TRIAL OF THE O'NEIL LONG ACTING NALTREXONE IMPLANT**
Overview:	A Phase I/II, Single Arm, Open Label study measuring the Pharmacokinetics of the O'Neil Long Acting Naltrexone Implant (OLANI). This study will examine the pharmacokinetic profile of OLANI over 540 days in participants without a DSM 5 - Substance Related Disorders classification. Participants will be required to undergo a Naloxone Challenge Test (NCT) to confirm opiate naivety before administration of the study medication. All participants will be treated with a double administration of a 1.8g ([redacted]) OLANI in an open label manner. No randomization will occur.
Objectives:	**Primary:** To characterize the pharmacokinetic profile (C_{max}, T_{max}, AUC, T>MEC, where MEC = 1.33 ng/mL NTX, Time to C_0 for naltrexone) of the OLANI (2 units). Primary outcomes used to determine these properties will be based on results from plasma concentration of naltrexone and 6-β-naltrexol as ascertained from blood samples taken at the following time points: – 0, 3, 6, 12, 24, 48 hours – 4, 8, 14, 21, 28, 35, 42, 49, 56, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510 & 540 days. Note: 1.33 ng/mL is a target MEC for this protocol. The MEC will be further developed over time. **Secondary:** • To characterize the safety profile (i.e. adverse events, laboratory results, wound site and inflammatory response rates) of the OLANI.
Endpoint:	***Primary:*** The collection of at least 75% pharmacokinetic blood time points including 2 consecutive monthly naltrexone blood levels recorded at <0.1 ng/mL in 10 participants. ***Primary Efficacy Endpoint:*** Proportion of participants who tolerate OLANI and maintain blood level of naltrexone of at least 1.33 ng/mL at all collected time points to ≥180 day time point.
Population:	20 healthy participants (10 male, 10 female), aged between 18 and 55 years old, without a DSM 5 - Substance Related Disorders classification.

Phase:	I/II
Number of Sites:	One site: Substance Use Research Centre (SURC), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA (initial assessment, follow up to 48 hours, Final Visit or Early Termination Visit, and additional follow up visits as appropriate) Satellite Location 1: Columbia University Medical Center (CUMC), 177 Fort Washington Ave., New York, NY 10032, USA (IP administration) Satellite Location 2: Clinilabs, 423 West 55th St, New York, 10019 (post 48 hour follow-up)
Investigational Product:	The investigational product is the O'Neil Long Acting Naltrexone Implant (1.8g, [redacted]) x 2 units. The investigational product is a biodegradable implant which is administered subcutaneously using a minor surgical procedure under local anesthetic.
Study Duration:	Estimated 22 months
Participant Duration:	540 days

VI. SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

1.1 SPONSOR

Go Medical Industries Pty Ltd,
200 Churchill Ave, Subiaco, Perth, WA 6008, Australia

1.2 PRINCIPAL INVESTIGATOR

Adam Bisaga M.D.
New York State Psychiatric Institute, 1051 Riverside Dr., New York, NY 10032

1.3 INSTITUTE

Substance Use Research Center (SURC), New York State Psychiatric Institute, 1051 Riverside Dr., Unit 120, New York, NY 10032 (Initial assessment, follow up to 48 hours, Final Visit or Early Termination Visit, and additional follow up visits as appropriate)

1.3.1 SATELLITE LOCATION 1

Columbia University Medical Center (CUMC), 177 Fort Washington Ave., New York, NY 10032 (IP administration)

1.3.2 SATELLITE LOCATION 2

Clinilabs, 423 West 55th St, New York, 10019 (post 48 hour follow-up)

1.4 CLINICAL LABORATORY

PK analysis of naltrexone and 6- β-naltrexol will be performed by a qualified bioanalytic laboratory. No other clinical labs will be performed.

1.5 CENTRAL CLINICAL LABORATORY

(LFT, FBC, EUC, URINE DRUG SCREEN AND ROUTINE PATHOLOGY)
Laboratory Corporation of America

1.6 RESPONSIBLE CLINICIAN

Adam Bisaga M.D.
New York State Psychiatric Institute, 1051 Riverside Dr., New York, NY 10032

1.7 IMPLANTATION PROCEDURE SURGEON

Christine Rohde, MD, MPH, FACS
Associate Professor of Surgery at CUMC
Board Certified in Plastic Surgery
Chief of Microvascular Services, Department of Surgery
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1.8 SPONSOR REPRESENTATIVE

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1.10 CLINICAL TRIAL CO-ORDINATOR

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1.11 STATISTICIAN

Provided by Clinilabs, 423 West 55th St, New York, 10019

1.12 CLINICAL RESEARCH ASSOCIATE

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC

2.1 BACKGROUND INFORMATION

Naltrexone (NTX) is a synthetic derivative of thebaine, a minor constituent of opium. It is a nonspecific pure opioid antagonist. NTX binds competitively to all classes of opioid receptors with the following order of preference μ>κ>δ, with a high affinity for the μ-opioid receptor. It blocks the effects of opioids by competitive binding at opioid receptors. NTX is approved by the FDA for the treatment of opioid dependence/opioid use disorder (OUD) and is also approved for the treatment of alcohol use disorder. NTX is currently registered in USA as a once daily oral formulation containing 50 mg of NTX and as a once-monthly injectable formulation containing 380 mg of NTX.

2.1.1 Metabolism of Naltrexone

NTX is well absorbed orally (96%), but it undergoes a significant first pass metabolism resulting in only 5 to 40% oral bioavailability. Naltrexone is extensively metabolized in humans[1]. Production of the primary metabolite, 6β-naltrexol (6-BN), is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. Two other minor metabolites are 2-hydroxy-3-methoxy-6β-naltrexol and 2-hydroxy-3-methoxy-naltrexone[2]. NTX and 6-BN terminal half-life values have been reported as ranging from 2 to 10 hours for naltrexone[3–5] and 7.5 to 13 hours for 6-BN[3,5,6]. Both NTX and 6-BN are excreted primarily by the kidneys. There is a large amount of variation in the metabolism and pharmacokinetics of NTX. In one study, the enzyme kinetics of the formation of 6-BN from NTX using human liver cytosol preparation showed a 2.9 fold variability in Vmax, a 3.2 fold variability in Km and a 7.7 fold variability in intrinsic clearance[7]. The systemic clearance of NTX supersedes the hepatic blood flow, suggesting the NTX is highly extracted and extra hepatic sites of drug metabolism exist.

2.1.2 Clinical Use of Naltrexone

While NTX is a potent antagonist and efficiently blocks the effects of exogenous opioids such as heroin, the success of NTX for the treatment of opioid dependence has been limited by poor patient compliance with the oral formulation[8]. Unlike alternative pharmacotherapies for opioid dependence such as methadone and buprenorphine, NTX has no positive reinforcing effects, ceasing NTX has no withdrawal or negative consequences. Thus there is little incentive to continue taking the oral formation, with patients often stopping the medication and returning to opioid use. After opioid detoxification, patients are likely to have reduced tolerance to opioids. As the blockade of exogenous opioids provided by NTX wanes and eventually dissipates completely, patients who have been treated with NTX may respond to lower doses of opioids than previously used, just as they would shortly after completing detoxification. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.) if the patient uses previously tolerated doses of opioids[9].

Better NTX compliance has been observed when a responsible adult is available to supervise daily NTX dosing[10]. It has been reported that the method of daily oral NTX treatment is not an affective long term treatment in most patients[11,12]. Clinical data has indicated that poor medication compliance occurs with daily oral NTX maintenance treatment for opioid dependence[8,10,13]. It has been proposed that the development of a sustained release NTX preparation would combat these issues and lead to improved outcomes for opioid users.

2.1.3 Sustained Release Preparations

Wise (1984) developed a NTX (70%)-poly(D,L-lactide-co-glycolide) copolymer (30%) implant[14], which was the first biodegradable drug delivery system approved by the Food and Drug Administration (FDA) for clinical testing, but was limited by "burst release" in human trials. Previous findings also suggested that polymeric NTX sustained release systems are biocompatible formulations[15,16]. Additionally, several dosage forms have also been proposed. For example, a NTX-poly(lactic acid) composite[17], which had an effective blocking action to morphine in rats for 24 days; NTX-copolymer (90% L-lactic acid and 10% glycolic acid) beads[18],which would provide constant NTX levels for one month, and a NTX pamoate linear poly(ortho esters) disk[19], which released NTX pamoate for 21 days. In 2006, Alkermes registered a 30 day NTX intramuscular injection known as Vivitrol with the FDA for treatment of alcohol dependence, and it was also approved by FDA in 2010 for the treatment of opioid dependence[20,21]. Vivitrol consists of a NTX PLGA microsphere suspension delivered intramuscularly via an injection. Some studies revealed that a 380 mg injection can produce a blood NTX level of 1.2 ng/mL for approximately four weeks[22]. However, Vivitrol has been found to give dose-dependent effects with some adverse events[23].

2.1.4 Investigational Product: O'Neil Long Acting Naltrexone Implant (OLANI) – In Vitro Information

Basic composition of the OLANI formulations is a proprietary combination of [redacted].

The manufacturing process has been developed from its original laboratory scale and refined to more commercial Good Manufacturing Practice (GMP) techniques via a process of upscaling. Therefore, the investigational product has evolved into two generations of product. The first generation of investigational product was manufactured under smaller scale R&D production. Initially the manufacturing tolerances for early investigational product were reflective of manufacturing capability and were set as [redacted].

During product development and upscaling, the manufacturing process was improved to allow for more commercially sized manufacturing equipment to be implemented and a reduction in residual solvent levels in the final product. The variation itself consists of [redacted].

The second generation of product using the [redacted].

Continual product improvement has now allowed for the second generation spray coated product specification [redacted].

Preliminary water bath data demonstrates that the release rates for both generations of implants are very similar [redacted]. Data generated from water bath experiments that demonstrates similar release rates between the old and new formulations, suggests that the risk of variations to the efficacy and safety of the new product is low.

The biodegradable polylactic based polymer is used in a variety of products e.g. [redacted], with the authors estimating an incidence of foreign body reaction of 4.9%, from accumulated data from 412 patients.

In-vitro dissolution experiments were conducted with a standardized method. [redacted] Figure 2.1 includes a comparison between the initial release rates of the first and second generation products.

[redacted]

Figure 2.1: Comparison of release rate of spray coated (second generation) vs dip coated (first generation), release specification limits highlighted

Dissolution data indicates appropriate sustained release characteristics maintained for over six months and satisfactory batch-to-batch consistency. The variation between manufacturing formulation for first and second generation implants is not considered to be significant as

demonstrated by the water bath release rate data being similar and well within the release rate limits. Release rate limits of both generation implants are similar.

2.1.5 OLANI: Clinical Trials

A number of clinical trials have been conducted on the OLANI in collaboration with the University of Western Australia and the Norwegian Centre for Addiction Research into efficacy, safety and pharmacokinetics of the implant preparation. The earlier trials (GM 008, GM 009 & NCT 00521157) all used the first generation [redacted]; see Table 2-1. GM 012 used the second generation [redacted] with the early release specifications of 0.6 to 10mg/day of NTX between days 14 and 21. GM 012 was suspended early due to unacceptable inflammatory reactions that were observed. It is believed that the higher number of inflammatory reactions observed from the batch of second generation implants used in this trial occurred due to the change in manufacturing process in conjunction with the retention of the original wide release rate tolerance range of [redacted].

In a review of all ADR & SAE reported at the AMPRF clinic for where patients received treatment under the Special Access Scheme (SAS), between Feb 2016 – Jan 2017 (see 2.1.6.2), the rate of inflammatory response was 11.44% (507/58), as the majority of these were either mild or treated with oral prednisolone, the number of implants removed due to unresolved inflammatory response was only 1.18%.

The current 2nd generation OLANI under investigation has a release rate specification of [redacted]

Table 2-1: List of Clinical Trials Performed During the Development of OLANI

Trial Number	Trial Name	Phase	Investigational Product	Dosing	Type of Study	HREC
GM 008	A Randomised Double-Blind Placebo Controlled Clinical Trial of The Efficacy of an Australian Naltrexone Implant Compared to Oral Naltrexone for The Long-Term Management of Heroin Dependent Persons.	II/III	[redacted]	2 Implants*	Safety & Efficacy	RA/4/1/ 0739
GM 009	A Phase I, Single Arm, Open Label, Pharmacokinetic Trial of The O'Neil Long Acting Naltrexone Implant Over 6 Months in a Small Cohort of Opioid Dependent Persons (PK Study)	I	[redacted]	2 Implants	PK	RA/4/1/ 1554
NCT 00521157	Naltrexone Implants After In-Patient Treatment for Opioid Dependence: Randomised Control Trial	II/III	[redacted]	2 Implants	Safety & Efficacy	
GM 012	An open-label, phase 3 study of the safety of the O'Neil Long Acting Naltrexone Implant treatment for substance dependence	III	[redacted]	≤ 62kg = 2 implants > 63kg = 3 implants	Safety	RA/4/1/ 2310

*Due to blinding, each implant treatment consisted of 20 NTX tablets, divided over three syringes. Two syringes contained 8 NTX tablets flanked by two placebo tablets. The third implant syringe contained 4 NTX tablets flanked by two placebo tablets.

2.1.6 Clinical Use Summary

2.1.6.1 Compassionate Use Programs

Compassionate use programs such as the SAS in Australia have allowed for the clinical use of the OLANI in patients determined to be at high risk of premature death. The OLANI is used for patient indications of opioid, alcohol and amphetamine dependency. In order to qualify for treatment under the SAS, patients must provide informed consent and be assessed by a medical practitioner.

Routine clinical and laboratory follow-up of AMPRF patients has included assessments of wound health, implant tolerance, general wellbeing, opioid craving and blood naltrexone (NTX) concentrations (to confirm continuing opioid resistance and judge the requirement for repeat implantation). Approximately 50% of patients return for follow-up treatments demonstrating a good level of patient perception of efficacy. Many patients have continued to self-refer for further treatment over a number of years.

From 2006 to January 2018, approximately 5,369 treatments were carried out, with a mean dose of 2.61 implants per procedure (total number of OLANI 14,032). The second generation product has had three main batch prefix codes (NTXA, GOPS and GM), based on the manufacturing facility and its time in the product development pathway. All implants manufactured at the present facility under GMP have the "GM" prefix batch code. Table 2-2 shows the total number of patients treated with the second generation OLANI, broken down by manufacturing period and by treatment indication. Go Medical has manufactured the current formulation in its GMP facility since 2015 and has been used clinically since February 2016.

Table 2-2: Total number of second generation OLANI used sorted by treatment

Indication treated	Total Treatments	Total No. Patients	Average Age [Std Dev]	Female %	Male%	Total number of OLANI *(Syringes)	Average Dose [Std Dev]
NTXA							
Alcohol	135	101	39.71 [10.59]	35%	65%	381	2.82 [0.62]
Amphetamines	40	35	32.21 [7.51]	21%	79%	108	2.70 [0.69]
Opiates	1041	720	34.91 [8.07]	35%	65%	2654	2.55 [0.66]
NTXA Total	**1216**	**856**	**35.36 [8.51]**	**35%**	**65%**	**3143**	**2.58 [0.67]**
GOPS							
Alcohol	500	340	41.47 [11.20]	34%	66%	1414	2.83 [0.60]
Amphetamines	819	584	32.20 [8.02]	28%	72%	2374	2.90 [0.62]
Opiates	1754	1033	35.69 [8.77]	33%	67%	4213	2.40 [0.67]
GOPS Total	**3075**	**1959**	**35.70 [9.49]**	**32%**	**68%**	**8008**	**2.60 [0.68]**
GM							
Alcohol	166	134	41.45 [11.60]	33%	67%	470	2.83 [0.50]
Amphetamines	399	324	33.76 [8.54]	27%	73%	1136	2.85 [0.56]
Opiates	515	404	38.51 [9.97]	27%	73%	1282	2.49 [0.62]
GM Total	**1080**	**862**	**37.21 [10.14]**	**28%**	**72%**	**2888**	**2.67 [0.61]**
Grand Total	**5369**	**3675**	**35.92 [9.44]**	**31%**	**69%**	**14032**	**2.61 [0.67]**

*Each syringe contains ≈1.86g of naltrexone. It should be noted that the average dose given to alcohol and amphetamine patients is greater than the dosing for opioid patients.
NTXA = prefix for batches manufactured at the original Go Medical facility under GMP between 2009-2011
GOPS = prefix for batches manufactured under an extemporaneous compounding law between 2011-2015
GM = prefix for batches manufactured at the present Go Medical facility under GMP since 2015

2.1.6.2 2nd Generation OLANI ADR & SAE Review

A review was carried out on all of the ADR and SAE data collected from February 2016 – January 2018 for patients treated at AMPRF with the 2nd generation OLANI manufactured under full GMP (prefix "GM").

The majority of patients presenting to AMPRF for treatment are patients with an Opiate or Amphetamine (predominantly methamphetamine) use disorder, with a smaller number being treated for an alcohol use disorder. As these conditions have related comorbidities expected, ADR & SAE data is presented for patients (#treatments =515) presenting with an opiate use disorder. All ADRs and SAEs were categorized as per Figure 2.2 and are presented in Table 2-3.

A breakdown for all ADR's and SAE's by ICD10 description is presented in Table 2-4 and Table 2-5.

Figure 2.2: Causality Groups

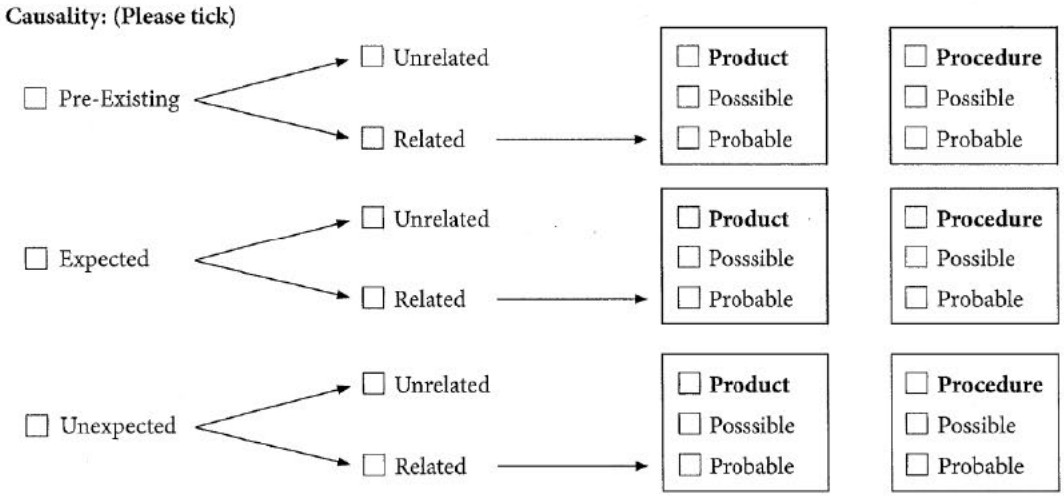

Table 2-3: Opiate Treatments ADRs and SAEs reported between February 2016 and January 2018 for GM 2nd Generation OLANI's

Causality	Count of Events	% of Total Events	Count of Unique Events	% of Unique Events
Pre-Existing – Related Procedure	0	0.00%	0	0.00%
Pre-Existing - Related Product	10	2.97%	10	3.60%
Pre-Existing - Unrelated	25	7.42%	23	8.27%
Expected - Related Procedure	3	0.89%	3	1.08%
Expected - Related Product	189	56.08%	138	49.64%
Expected - Unrelated	0	0.00%	0	0.00%
Unexpected - Related Procedure	4	1.19%	4	1.44%
Unexpected - Related Product	8	2.37%	8	2.88%
Unexpected - Unrelated	98	29.08%	92	33.09%
Grand Total	**337**		**278**	

Table 2-4: Opiate Treatment ADRs by ICD10 description.

ICD Description	No. of Events	Total Events %	Unique Events	Unique Events %
Expected - Related Procedure	**3**	**0.93%**	**3**	**1.14%**
Infected Implant	1	0.31%	1	0.38%
Wound Disruption, Unspecified	1	0.31%	1	0.38%
Inflammatory Reaction	1	0.31%	1	0.38%
Expected - Related Product	**187**	**58.07%**	**136**	**51.71%**
Inflammatory reaction due to implants	96	29.81%	54	20.53%
Withdrawal State - Opioids	35	10.87%	32	12.17%
Depression (Recurrent Depressive Episodes)	16	4.97%	15	5.70%
Insomnia	16	4.97%	12	4.56%
Anxiety	15	4.66%	14	5.32%
Implant Removal - Inflammatory Response	5	1.55%	5	1.90%
Implant Removal - Other Reason	1	0.31%	1	0.38%
Suicidal ideations	1	0.31%	1	0.38%
Erectile Dysfunction	1	0.31%	1	0.38%
Diarrhea, unspecified	1	0.31%	1	0.38%
Pre-Existing - Related Product	**10**	**3.11%**	**10**	**3.80%**
Anxiety	5	1.55%	5	1.90%
Depression (Recurrent Depressive Episodes)	4	1.24%	4	1.52%
Insomnia	1	0.31%	1	0.38%
Pre-Existing - Unrelated	**22**	**6.83%**	**20**	**7.60%**
Unexpected - Related Procedure	**3**	**0.93%**	**3**	**1.14%**
Chest pain, unspecified	1	0.31%	1	0.38%
Unspecified adverse effect of drug or medicament	1	0.31%	1	0.38%
Overdose, Unspecified	1	0.31%	1	0.38%
Unexpected - Related Product	**7**	**2.17%**	**7**	**2.66%**
Dermatitis, unspecified	1	0.31%	1	0.38%
Wound Disruption, Unspecified	1	0.31%	1	0.38%
Unspecified fall	1	0.31%	1	0.38%
Erectile Dysfunction	1	0.31%	1	0.38%
Poisoning by benzodiazepines	1	0.31%	1	0.38%
Other	1	0.31%	1	0.38%
Suicidal ideations	1	0.31%	1	0.38%
Unexpected - Unrelated	**90**	**27.95%**	**84**	**31.94%**
Influenza, Virus Not Identified	9	2.80%	7	2.66%
Other Depressive Episodes	5	1.55%	4	1.52%
Suicidal ideations	5	1.55%	4	1.52%
Poisoning by, Narcotics and Psychodysleptics	4	1.24%	4	1.52%
Injury	4	1.24%	4	1.52%
Other infective otitis externa, bilateral	3	0.93%	2	0.76%
Chest pain, unspecified	3	0.93%	3	1.14%
Migraine, unspecified	3	0.93%	3	1.14%
Asthma	3	0.93%	2	0.76%
Other*	51	15.84%	51	19.39%
Grand Total	**322**	**100.00%**	**263**	**100.00%**

Table 2-5: Opiate Treatment SAE's by ICD10 description.

ICD Description	No. of Events	Total Events %	Unique Events	Unique Events %
Expected - Related Procedure				
Implant Removal - Infection	1	6.67%	1	6.67%
Staphylococcal Infection, Unspecified Site	1	6.67%	1	6.67%
Expected - Related Procedure Total	**2**	**13.33%**	**2**	**13.33%**
Expected - Related Product				
Inflammatory reaction due to implants	1	6.67%	1	6.67%
Expected - Related Product Total	**1**	**6.67%**	**1**	**6.67%**
Pre-Existing - Unrelated				
Grand Mal Seizure / Tonic Clonic, Epileptic	2	13.33%	2	13.33%
Other psychoactive substance use, unspecified with psychoactive disorder	1	6.67%	1	6.67%
Pre-Existing - Unrelated Total	**3**	**20.00%**	**3**	**20.00%**
Unexpected - Related Procedure				
Car driver injured in collision, non-traffic accident	1	6.67%	1	6.67%
Unexpected - Related Procedure Total	**1**	**6.67%**	**1**	**6.67%**
Unexpected - Unrelated				
Bronchiectasis	1	6.67%	1	6.67%
Dissociative identity disorder	1	6.67%	1	6.67%
Fracture of lower leg, including ankle	1	6.67%	1	6.67%
Injury	1	6.67%	1	6.67%
Other Mental and Behavioural Disorders	1	6.67%	1	6.67%
Other seizures	1	6.67%	1	6.67%
Severe persistent asthma	1	6.67%	1	6.67%
Suicidal ideations	1	6.67%	1	6.67%
Unexpected - Unrelated Total	**8**	**53.33%**	**8**	**53.33%**
Grand Total	**15**	**100.00%**	**15**	**100.00%**

2.1.6.2.1 Inflammatory Reaction, Infection and Implant Removal

The highest number of ADR and SAE's were recorded as an 'Inflammatory reaction due to implants'. Patients are encouraged to see the doctor if a suspected inflammatory reaction is reported, with the standard treatment being oral treatment (prednisolone 50mg daily for 7 days). Due to the type of patients that are treated at AMPRF with the OLANI, not all patients will seek treatment early due to a number of factors that are usually related to their drug use lifestyle. Therefore, it can be common for patients to present to the AMPRF clinic after such time that a severe inflammatory response has occurred, which may result in the need for drainage of fluid that has built up. The fluid is sent for testing to ensure that the inflammation is not caused by a bacterial infection. In some cases, individual tablets of the OLANI will have been or are in the process of being excreted by the body. In such cases, the wound site will be cleaned and dressed to ensure that infection is minimized.

A breakdown of the number of treatment received by patients recorded as having an inflammatory response due to the OLANI is presented in Table 2-6.

Table 2-6: Treatment of AEs & SAE's reported as 'Inflammatory reaction due to implants'

Inflammatory Treatment	No. of Events	Total Events %	Unique Treatment Events*	Unique Treatment Events %
None	19	18.63%	16	21.92%
Oral Treatment	73	71.57%	47	64.38%
Fluid Drainage/Site cleaned	5	4.90%	5	6.85%
Non-Surgical Implant Removal	3	2.94%	3	4.11%
Surgical Removal	2	1.96%	2	2.74%
Grand Total	**102**	**100.00%**	**73**	**100.00%**

*Unique treatment events recorded the number of patients receiving the type of treatment. As a patient may receive oral treatment and then subsequently have fluid drainage, two unique treatment events would be recorded.

The majority of patients (73) received oral treatment which in most cases required only a single course of treatment to resolve the inflammation.

A total of 5 patients required fluid drainage/site cleaning alongside oral treatment to help resolve the inflammation.

There were a total of 3 patients recorded as having a 'Non-Surgical Implant Removal'. The term 'Non-Surgical Implant Removal' is used to refer to situation where partial (single or multiple tablets) removal of an implant has occurred that has not required surgery. This typically occurs when a large amount of fluid has built up due to the inflammatory response and either; during the course of draining of the fluid by the doctor individual tablets are also removed; or as part of the immune response individual tablets have been self-ejected through the original implantation wound site.

Where the inflammatory response is unresolved by initial treatments or a patient has not been treated through AMPRF, the OLANI's have been surgically removed under general anaesthetic within a hospital setting. A total of 2 patients were recorded as having their implants surgically removed because of an inflammatory response. This represents a removal rate of 0.38 per treatment episode (2 in 515).

There were a further two cases of surgical removal not related to inflammatory response.

One case was recorded as due to infection of the OLANI site. As the case was reported 131 days post implantation procedure, it is unlikely that the infection was caused by the OLANI or implantation procedure. It is most likely that this was an inflammatory response to the OLANI, however as the patient was not referred for the procedure via AMPRF it is difficult to prove that this was the case.

The second case was recorded as due to psychological reasons, as the patient had requested for the OLANI to be removed as they could not function in their daily activities (Patient reported continued use of high dose opiates).

2.1.6.2.2 Conclusions

The ADR and SAE's data reported that the majority of events were due to inflammatory reactions, with about 11.26% (58 in 515) of treatments recording an inflammatory reaction. Of these, the majority could be classified as mild enough to require no further intervention or to be managed with standard oral treatment (prednisolone). Only 1.94% (10 in 515) of treatments could be classified as being more severe and requiring greater intervention of;

'fluid drainage/site cleaned' 0.97% (5 in 515), 'non-surgical removal' 0.58% (3 in 515) or surgical removal 0.38% (2 in 515).

The majority of inflammatory reports occur within the first 60 days of implantation with peak values around the 56 day mark. It should also be noted that this data represents reports of inflammatory reactions received by AMPRF either through proactive follow up questionnaires or patients reporting issues to the clinic. Natural attrition of follow up will occur over a period of 365 days and thus the reported inflammatory responses may be under reported in the latter period of the follow up.

After inflammatory reactions, the next most common ADR was related to withdrawal state - opiate 6.21% (32 in 515) and other associated drug withdrawal symptoms (Insomnia, Anxiety, Depression and Nausea) 7.96% (41 in 515).

Overall it can be concluded that the OLANI is safe and that the perception of efficacy amongst patients has outweighed any perceived inconvenience arising from the mild inflammatory reactions that have been observed. A method for treatment of inflammatory responses is effective with only a small amount of procedures requiring removal of an implant for an unresolved inflammatory response. It is also important to have good treatment plans in place to help patients post implantation to deal with the expected withdrawal symptoms and adjustment to a change in lifestyle from opiate dependence.

2.2 STUDY RATIONALE

To date, a number of studies have been carried out on the first generation of the OLANI measuring PK, efficacy and safety data. The current study seeks to collect pilot PK data on the second generation OLANI in healthy participants without a DSM 5 - Substance Related Disorders classification. The use of healthy non-substance dependent volunteers for this protocol greatly reduces the risk of opioid withdrawal related AE's and opioid overdose due to sub-therapeutic naltrexone blood levels being recorded. This pilot data will be used in the planning and design of a large bioequivalence study on the OLANI.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 Known Potential Risks

1. When the local anesthetic used during OLANI insertion wears off, the site of implantation may be tender.
2. The OLANI may cause irritation or inflammation at or near the site of administration as a result of an allergic response or other inflammatory process.
3. There is a risk of infection with any surgical procedure of this type. The risk is minimized by use of appropriate sterile technique and ensuring that the formulation meets normal pharmaceutical standards for sterility.
4. In the unlikely event the participant requires narcotic painkillers for severe pain; most will have a greatly reduced effect whilst naltrexone is still being released from the OLANI and higher doses of high potency opioids may need to be used. In instances where pain cannot be controlled by other means (such as regional blocks or alternative drugs see section 7.7) the OLANI may have to be removed surgically.

5. Known side-effects from naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, join and muscle pain, headache, loss of appetite, diarrhea, constipation, increased thirst, increased energy, depressive mood, irritability, dizziness, skin rash, delayed ejaculation, erection dysfunction, reduced sexual desire, and chills.
6. Naltrexone has been associated with reversible hepatocellular injury indicated by elevated liver enzymes when administered at doses substantially greater than the doses expected in this study. When used in the lower dose range in opiate dependent patients, this risk is remote[26,27]. Naltrexone is therefore contraindicated in participants with acute hepatitis or liver failure, and such participants are excluded from the study. Participants with hepatic enzyme levels greater than three times the upper limit of normal are excluded. Implantable naltrexone achieves lower blood levels than oral naltrexone initially, and blood level should remain lower throughout treatment period than levels associated with hepatitis. If naltrexone induced hepatitis were to occur in the setting of long-acting preparation, where the naltrexone would be only very slowly eliminated, this would prolong exposure to the offending agent. However, the experience with injectable and implantable naltrexone also suggests it is safe. In studies with injectable naltrexone several participants experienced elevation in liver enzymes, which were determined to be related to hepatitis C. Several recent reports with injectable naltrexone showed that it poses significantly lower risk of hepatotoxicity than previously suspected, even among alcohol and opioid-dependent persons including those with HCV and/or HIV infection[28–31]. In July of 2013, the Boxed Warning on the hepatotoxicity was removed from the Vivitrol Package Insert."
7. Naloxone injection may cause withdrawal symptoms such as nausea, vomiting, diarrhea, stomach pain, fever, sweating, body aches, weakness, running nose, goosebumps, shivering, increased heart rate, and anxiety.

2.3.2 Known Potential Benefits

1. There are no known potential benefits of this treatment in the study cohort.
2. There is a large potential benefit to the opiate addicted community should the PK pilot study provide strong pharmacokinetic data which would aid in getting a long term naltrexone product through the registration process and onto the market.

3 OBJECTIVES AND PURPOSE

3.1 PRIMARY OBJECTIVES

To characterize the pharmacokinetic profile (C_{max}, T_{max}, AUC, T>MEC, where MEC = 1.33 ng/mL NTX, Time to C_0 for naltrexone) of the OLANI (2 units).

Primary outcomes used to determine these properties will be based on results from plasma concentration of naltrexone and 6-β-naltrexol as ascertained from blood samples taken at the following time points:

- 0, 3, 6, 12, 24, 48 hours
- 4, 8, 14, 21, 28, 35, 42, 49, 56, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510 & 540 days.

Note: 1.33 ng/mL is a target MEC for this protocol. The MEC will be further developed over time.

3.2 SECONDARY OBJECTIVES

- To characterize the safety profile (i.e. AEs, laboratory results, wound site and inflammatory response rates) of the OLANI.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This pilot study is a phase I/II, open label, single-arm pharmacokinetic trial of the OLANI in healthy participants without a DSM 5 - Substance Related Disorders classification. PK data will be collected in all participants until 2 consecutive monthly naltrexone blood levels recorded at <0.1 ng/mL, it is anticipated that this will occur by Day 540. Participants will be required to undergo a Naloxone Challenge Test (NCT) to confirm absence of physiological dependence on opioids before administration of the study medication. Participants will be recruited, treated and followed up at the SURC clinic at the NYSPI.

All participants will be treated with a double administration of a 1.8g ([redacted]) OLANI.

4.2 STUDY ENDPOINTS

4.2.1 Primary Endpoint

- The collection of at least 75% pharmacokinetic blood time points including 2 consecutive monthly naltrexone blood levels recorded at <0.1 ng/mL, in 10 participants.

4.2.2 Secondary Endpoints

- Detailed PK characteristics of the product.
- The collection of safety information and AEs information over 540 days in participants treated with the OLANI.

4.2.3 Primary Efficacy Endpoint:

- Proportion of participants who tolerate OLANI and maintain blood level of naltrexone of at least 1.33 ng/mL at all collected time points to ≥180 day time point.

4.2.4 Secondary Efficacy Endpoints:

- Mean Cmax, Tmax, AUC for naltrexone blood level
- Mean T>MEC for naltrexone, where MEC = 1.33 ng/mL
- Mean Cmax, Tmax, AUC for 6β-naltrexol blood level
- Frequency of AEs and SAEs

4.2.5 Exploratory Efficacy Endpoints:

- Use of drugs (opioids, cocaine, marijuana) and alcohol, as reported by participants and detected using urine drug screen (UDS).

5 STUDY ENROLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Healthy participants without a DSM 5 - Substance Related Disorders classification will be recruited for this study. Participants will be assessed for their general health and mental health status.

Participants will be required to undergo a NCT to confirm opiate naivety before administration of the study medication. Participants will be required to not have had a naltrexone implant or any other extended release naltrexone preparation administered within the last year. A naltrexone blood sample will be taken at baseline to confirm zero naltrexone levels for data analysis.

To qualify for the study participation, participants must also be:

1. Men or women between the ages of 18 and 55 years old (inclusive)
2. Without DSM 5 - Substance Related Disorders classification; in sustained remission is not exclusionary
3. Able and willing to comply with the requirements of the protocol
4. Able and willing to provide written informed consent
5. Willing to undergo a minor surgical procedure under local anesthetic to allow for investigational drug administration in the subcutaneous tissue
6. Have an initial weight between 45.3 and 81.6 kilograms (inclusive) or have a BMI inclusive of 18.5 to 30.0

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Positive UDS at screening for illicit substances.
2. Is currently on naltrexone medication.
3. Has had a naltrexone implant in the past 24 months.
4. Has received treatment with an extended naltrexone product (e.g. Vivitrol) in the past 12 months.
5. Has a condition which requires treatment with opioid based medication.
6. Has a known hypersensitivity to naltrexone.
7. Has a known hypersensitivity to poly-lactic based materials e.g. biodegradable sutures, surgical implants or previous biodegradable implants.
8. Has a known hypersensitivity to local anesthesia.
9. 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.
10. Demonstrates any abnormal skin tissue in the proposed implantation area.

11. Is pregnant or planning to be. Women need to have negative blood pregnancy test at screening. Women need to agree to practice dual contraceptives.
12. Participant is breastfeeding or planning to be.
13. Has a current significant neurological (including cognitive and psychiatric disorders), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease unless currently controlled and stable with protocol-allowed medication 30 days prior to proposed investigational product administration.
14. Any clinically important abnormal finding as determined by medical history, physical examination, ECG or clinical laboratory tests.
15. 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.
16. ALT or AST > 3 times the upper end of the laboratory normal range.
17. Any methadone use 14 days prior to screening, and up to Study Day 0.
18. Current DSM 5 diagnosis of schizophrenia, bipolar, anxiety, or depressive disorder, confirmed by MINI assessment, or currently treated with medications for anxiety or depression. Past history (in remission DSM 5 classification) of anxiety or depression is not exclusionary.
19. 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)
20. Is participating or intending to participate in any other clinical trial during the duration of this study.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

5.3.1 Target Sample Size:

A total of 20 participants (10 females and 10 males) will be recruited. We expect that 10 of the 20 participants will complete the study (50%), which is providing at least 75% valid pharmacokinetic blood samples including 2 monthly naltrexone blood levels recorded at <0.1 ng/mL.

5.3.2 Recruitment

After reading the study consent participants will be seen by a research psychiatrist or psychologist for a screening evaluation and mental status examination as part of routine admission procedures at SURC. Final informed consent for the study will be obtained after full psychiatric and medical workup is complete. The research staff knows the protocol well and is able to explain study to the participant. Procedures for training staff physicians in each protocol and consent form include initial presentations by the Principal Investigator (PI) at weekly staff meetings, and weekly discussion of inclusion/exclusion criteria and study eligibility for each screening participant.

The use of the Contract Research Organization (CRO) Clinilabs, will also allow access to their participant database where the majority of healthy volunteers are expected to be recruited.

5.3.3 Retention

All participants will be reimbursed as per section 7.9 for each clinic visit to compensate them for the time spent doing research assessments as well as the cost of transportation. We will maintain a close phone contact with participants to confirm each visit, and to reschedule in case of the missed visit.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 Reasons for Withdrawal or Termination

- A participant may withdraw from the study at any time or for any reason without being obliged to divulge their reason for doing so to the investigators or clinic staff.
- A participant may be withdrawn from the study if there are unacceptable AEs, laboratory abnormality or any other medical condition or situation including distress due to effects of any study procedure or medication.
- A participant may be withdrawn from the study if in the opinion of the treating clinician the participant's interests are best served by withdrawing from the study.
- A participant may be withdrawn from the study if the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Participant will be withdrawn from the study if they fail the naloxone challenge test.

5.4.2 Handling of Participant Withdrawals or Termination

Participants, who do not receive the study medication (OLANI), for any reason, are not considered treatment failures. A participant may be discontinued from the study at any time if the participant, investigator, or sponsor determines that it is not in the best interest of the participant to continue participation. Reasons for discontinuation may include:

- Adverse event
- Withdrawal of participant
- Lost to follow-up
- Study terminated by investigator
- Pregnancy
- Clinical worsening
- Other
- Screen Failure

5.4.2.1 <u>Participant Monitoring and Removal from Study</u>

Medical staff will assess and communicate with the study PI the appropriateness for continuation in the research study on a continuous basis and will remove from the trial participants with significant clinical deterioration or noncompliance of a type which could be dangerous. Criteria for removal from the study will include:

1. Clinical deterioration which cannot be managed safely in the context of outpatient treatment. This would include a participant who becomes suicidal, or a participant

who goes on severe drug binges (including non-opiate drugs), endangering him/herself.

2. Elevation of liver enzymes > 3 times normal. The PI or a study physician is available 24 hours/day by phone and/or beeper in case of emergency.
3. Participant becomes pregnant. In case of incidental pregnancy, the participant will remain in the study and will be followed until the resolution of pregnancy. To reduce unnecessary procedures, we will stop PK blood draws, unless clinically indicated, however the safety monitoring will continue. In addition, we will collect safety information related to the pregnancy and birth outcomes. After finding an incidental pregnancy the removal of the implant will be offered to the participant and the participant will decide how best to proceed in consultation with her obstetrician. The decision regarding the pregnancy will affect the decision whether or not to remove the implant at any point during the pregnancy. The risk of anesthesia differs during different times during pregnancy, however the risks of anesthesia and the risks of removal are both minimal.

If a participant becomes pregnant, PK labs will no longer be collected, but the participant will be followed for safety monitoring for the remainder of the study.

For those who withdraw from the study, (data collection and / or treatment) there are two main options:

Option 1: Withdrawing from data collection and no further contact with study personnel. This carries the least amount of risk, with option 2 carrying some risk.

Option 2: Removal of the study medication via surgical procedure. Whilst removal of the study medication is straightforward in the early stages (up to about 10 days), removal after this becomes more complex as the OLANI biodegrades. Later procedures require a general anesthetic (with access to OR facilities) and may result in a large scar – certainly larger than not removing the implant but the extent depends on the amount of tissue to be excised. The risks associated with general anesthetic vary between people, but about 20% of those receiving general anesthesia have minor AEs and 0.2% have major AEs including death. If removal of the implant is the only acceptable option to the participant, this will be arranged through either Columbia University Medical Center or another local hospital.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to PI and sponsor. If the study is prematurely terminated or suspended, the PI will promptly inform the NYSPI IRB, (DSMB), FDA and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed; and satisfy the Sponsor, NYSPI IRB, DSMB and FDA.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 Acquisition

The OLANI will be supplied by Go Medical to the PI.

6.1.2 Formulation, Appearance, Packaging and Labelling

6.1.2.1 Manufacturing and Sterility

The OLANI is manufactured by Go Medical Industries Pty Ltd, 200 Churchill Ave, Subiaco, Perth, Western Australia, Australia 6008.

Tel: +61 (0)8 9388 1700, Email: info@gomedical.com.au

The OLANI is manufactured under the code of GMP. Sterilization (gamma) validation of the product at 25KGy is performed in accordance with ISO 11173. Implants are sterilized with gamma radiation between a minimum of 25KGy and no more than 40KGy. Regular crushed bioburden tests are also conducted on randomly selected samples from each batch. Pyrogen testing is also performed on sterilized product at routine periods.

6.1.2.2 Packaging

The OLANI is packed 10 pellets to one applicator device (Figure 6.1 and Figure 6.2). The applicator device is then sealed in a small foil pouch –Figure 6.3. This small foil pouch is then in turn sealed in another larger foil pouch –Figure 6.4. The double foiled pouch and applicator is labeled with a gamma indicator dot and the product label and sent for gamma sterilization. The gamma indicator dot will turn red when exposed to gamma radiation.

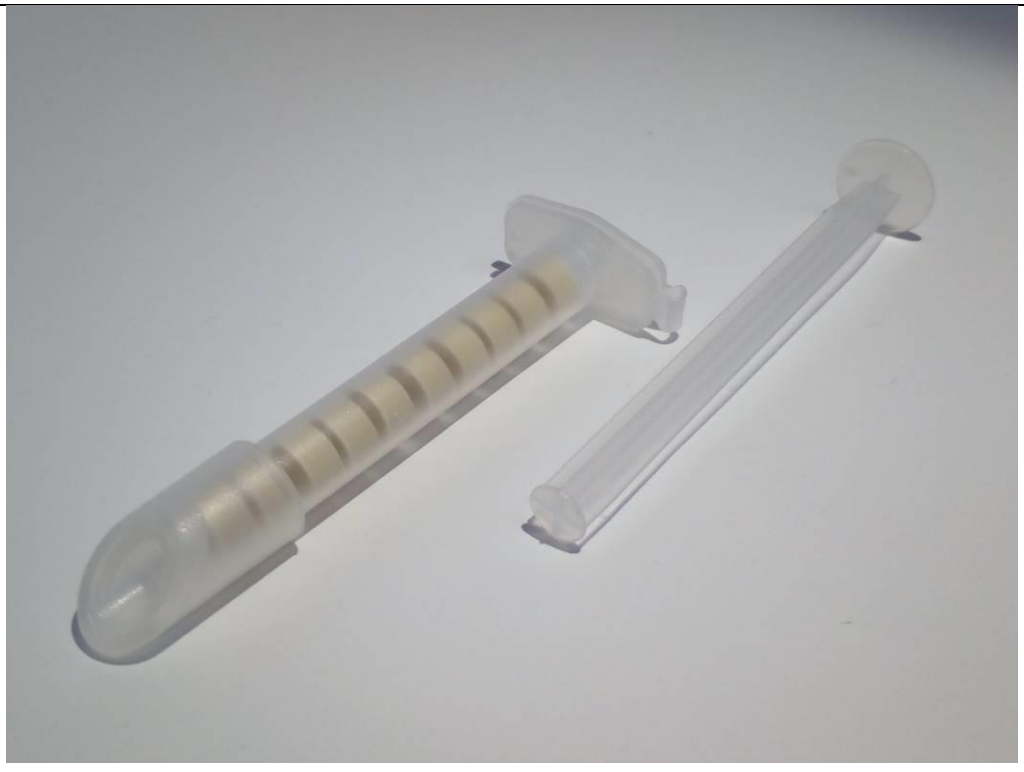

Figure 6.1: Applicator with OLANI pellets

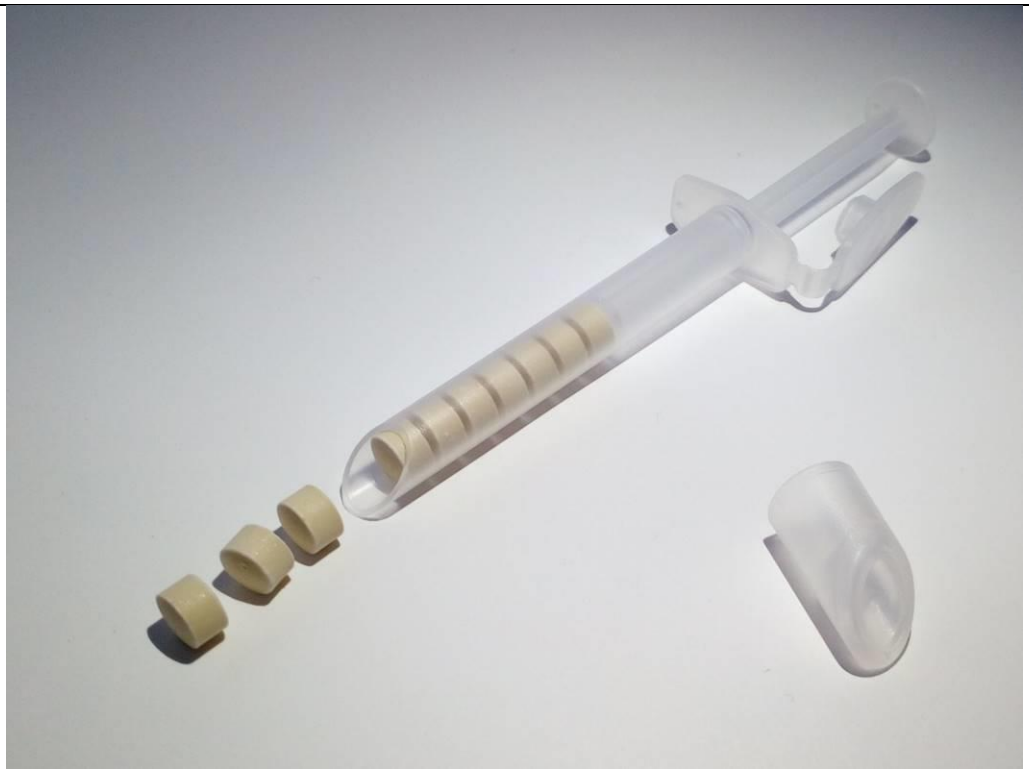

Figure 6.2: Applicator with tablets exposed for delivery

Figure 6.3: First layer packaging

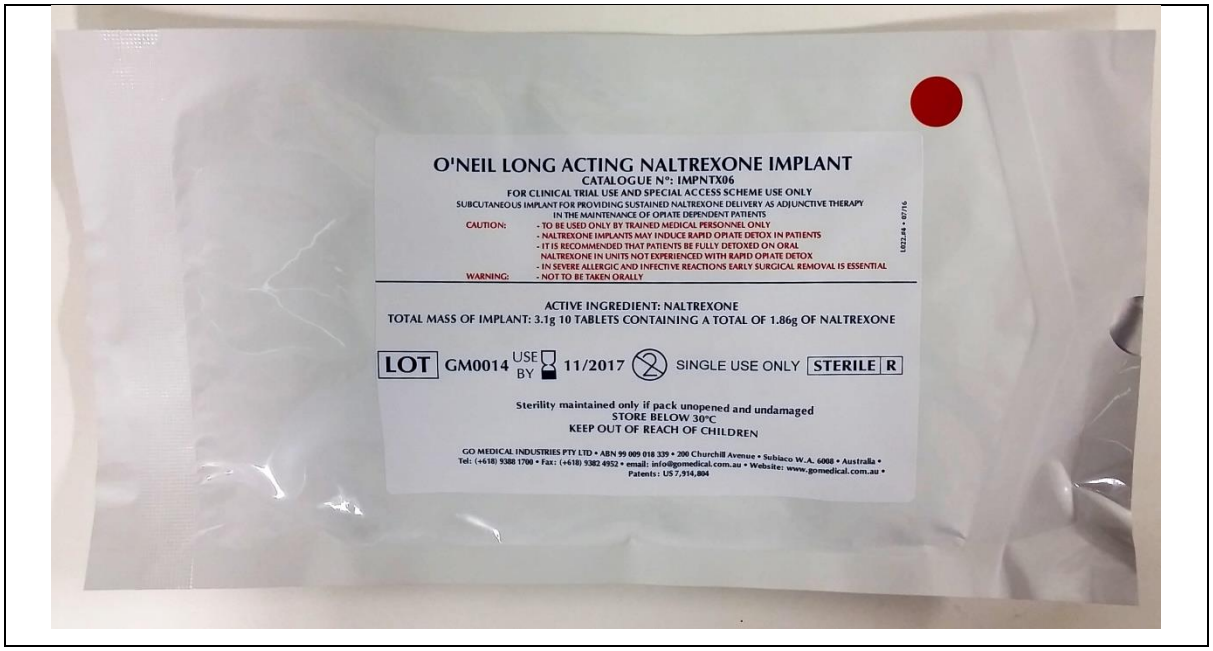

Figure 6.4: Second layer packaging

6.1.2.3 Disposal

The active implants shall be inserted into the subcutaneous tissue; however, the applicator device will be removed during the procedure and should be disposed of as per standard clinical protocols for biological specimens. The packaging can be disposed of in general waste.

6.1.3 Product Storage and Stability

The investigational product is supplied sterile in a double layer of foil packaging. Storage conditions require temperature to be maintained between 8-30°C. Expiration dates are 24 months from date of sterilization by manufacturer and are listed on the second layer of packaging.

6.1.4 Preparation

The investigational product is supplied sterile in foil packaging. The product will be prepared by the treating clinician using aseptic techniques to remove the applicator from the sterile packaging.

6.1.5 Dosing and Administration

All participants will be administered a double dose (two syringes with 10 tablets (1.8 g) each) of the OLANI ([redacted]). Investigational product will be administered surgically by the trial surgeon under local anesthetic. Subcutaneous insertion of the investigational product shall be documented as time = 0 for the purposes of pharmacokinetic blood collection.

6.1.6 Route of Administration

Subcutaneous implant via small surgical procedure conducted under local anesthetic.

6.1.7 Starting Dose and Dose Escalation Schedule

All participants will be administered the same starting dose of 2 x OLANI ([redacted], 1.8g).

6.1.8 Dose Adjustments/Modifications/Delays

Not applicable

6.1.9 Duration of Therapy

The duration of therapy will be 540 days.

6.1.10 Tracking of Dose

All participants will be implanted with the study dose. At each scheduled follow-up visit an implant site evaluation will take place.

6.1.11 Device Specific Considerations

Not applicable.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Go Medical will supply all study medication. The PI (or delegated study personnel) will sign that they have received all investigational product. Investigational product will be kept in a securely locked, temperature monitored cabinet and a drug inventory maintained. All unused supplies must be accounted for and returned to the sponsor in the event it is not used.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 Study Specific Procedures

7.1.1.1 Baseline Evaluation

Baseline evaluations will take place at the SURC, with two screening assessments being carried out, followed by a recruitment visit. The nature of the study and its risks and benefits will be explained to the participant by the PI who will also obtain a written informed consent from each potential participant prior to the administration of any study-specific procedures. The most important aspects of the protocol such as the implant procedure are discussed in great detail. The PI confirms that the participant is capable of providing informed consent.

At the first screening visit, informed consent for collecting information for screening will be obtained along with inclusion/exclusion criteria being assessed. The research physician will then perform tests as outlined in section 7.3.1.

At the second screening visit, medical staff or certified research assistants will collect blood and urine samples as outlined in section 7.3.2.

A recruitment visit will then be scheduled, where the research physician confirms that a participant meets all inclusion/exclusion criteria, is medically healthy to participate in the study. The physician also reviews and signs the inclusion/exclusion checklist and signs off on enrollment documentation. A procedure note for the medical chart will be included and signed verifying that the study physician reviewed results of the evaluation and obtained informed consent. Following study enrollment, the study physician assumes medical responsibility and arranging hospitalization for investigational product (IP) administration at CUMC followed by hospitalization at SURC.

7.1.1.2 Naloxone challenge test (NCT)

All participants will undergo a NCT at SURC prior to IP administration. Prior to administration of the NCT, a baseline Clinical Opiate Withdrawal Scale (COWS) assessment will be obtained. Participants will receive 0.8 mg naloxone, IM, followed by q10 minutes observation by research psychiatrist or nurse over 30 minutes for signs and symptoms of opiate withdrawal. A COWS assessment will be repeated 10, 20, and 30 minutes after the administration of the NCT. If any COWS score increases more than 2 points from baseline, the participant will be considered a NCT failure and will not receive the IP.

Naloxone injection may cause withdrawal symptoms such as nausea, vomiting, diarrhea, stomach pain, fever, sweating, body aches, weakness, running nose, goosebumps, shivering, increased heart rate, and anxiety. Most of these effects will wear off after 20-30 minutes and treatment is usually not needed but in case of severe symptoms, participants will be offered a dose of clonidine 0.1 mg and/or clonazepam 0.5 mg. In that case, participants will be monitored for up to 6 hours until all symptoms resolve, and they can be released.

If a participant passes the NCT then they will progress to the IP administration with the implantation procedure 7.1.1.3.

7.1.1.3 Implantation Procedure

The investigational product will be administered via a minor surgical procedure conducted at CUMC by the study surgeon Dr. Christine Rohde who is a board certified plastic surgeon. Prior to the procedure participants will be fitted with an intravenous cannula to aid blood collection during the first 48 hours of sampling. The surgical procedure will take approximately 30 minutes and will be performed under local anesthesia. The surgical procedure will be carried out by the study plastic surgeon trained in the implantation procedure (see 1.7) supported by a clinical nurse and another support staff.

Step 1: Have the participant lie on their back on an appropriate operating table

Step 2: Disinfect hands with approved validated procedures for the institution where the procedure is being carried out then apply non-sterile gloves.

Step 3: Administration of intra-operative prophylactic antibiotic. There is good literature evidence for intra-operative prophylactic antibiotics with breast and other implants. For this reason, the participant will be given 2g of IV cefazolin (600 mg clindamycin if allergic to cephalosporins or penicillin) within 30 minutes preceding the surgery.

Step 4: The participant's abdomen is carefully observed and palpated with a view to defining the most ideal surgical site. The usual placement of the OLANI is in V-shape (see Figure 7.1) with one implant on either side.

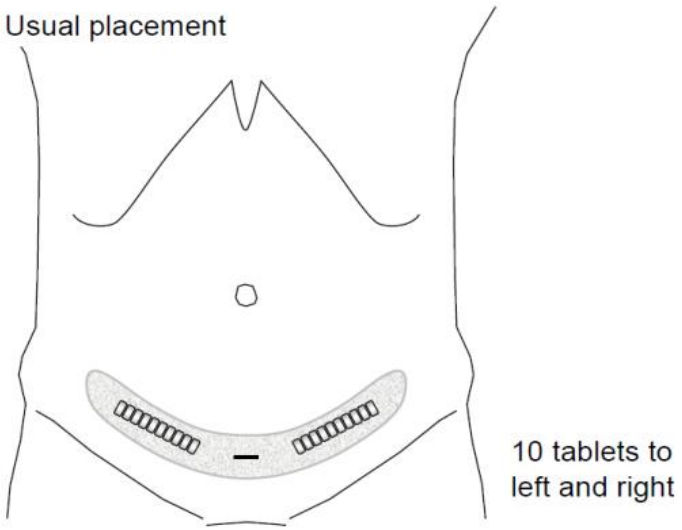

Figure 7.1: Usual OLANI placement

Step 5: Using a new disposable marker pen, define the area that the local anesthetic will be injected into (Figure 7.2). The outer limit of the anesthetic is defined by the outer lines and two single lines mark the center of the site. The two central lines guide the position that the original lidocaine is inserted into. The outer lines indicate the area that the 40 mL of bupivacaine is inserted into.

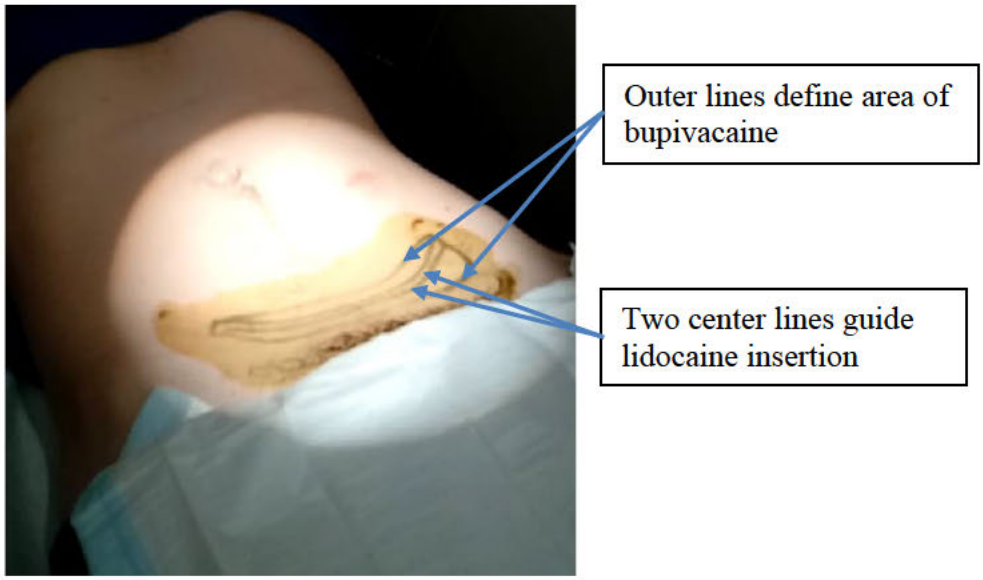

Figure 7.2: Target insertion of local anesthetic

Step 6: Following the drawing of the lines, the skin is prepared with betadine (or chloraprep if allergic to iodine). When this has dried a disposable sheet is applied carefully to cover the participant's underpants which will allow exposure of the symphysis pubis. Shaving can occur if any of the pubic or abdominal hair is close to the area marked.

Step 7: Administration of local anesthetic.

A total of 60 mL local anesthetic will be administered to cover the left and right-hand side of the abdomen. This shall consist of 20 mL of 0.5% lidocaine followed by 40 mL of 0.25% bupivacaine with adrenalin. The 20 mL of lidocaine is inserted initially with a 25 or 26 gauge needle very slowly along the marked two central lines. It is important to administer this very slowly to minimize the participant's discomfort. Initially 2mL is administered over several minutes without causing significant discomfort. After 2mL has been administered, remove the 25 or 26 gauge needle and change to a 1.5" or 2" (40 mm or 50 mm) 21 or 22 gauge needle. This new needle is carefully inserted into the subcutaneous tissues where the initial 2mL of local anesthetic had been inserted. 9mL of lidocaine can then be administered into the subcutaneous tissues on the left side of the abdomen and then the remaining 9mL can then be administered to the subcutaneous tissue on the right-hand side of the abdomen. The technique of inserting the initial 9 mL guided by the two marked central lines and the technique of pushing the subcutaneous tissues toward the needle allows the local anesthetic to be concentrated in the area between the sheath and the subcutaneous tissues. After the insertion of the lidocaine 20 mL of 0.25% bupivacaine with adrenaline is inserted into the subcutaneous tissue on the left side of the abdomen and another 20mL to the subcutaneous tissue right side of the abdomen to cover the area described in Figure 7.2.

Step 8: Preparation of the site following local anesthetic administration.

It is advised to wait 10 minutes following insertion of local anesthetic in order to maximize the benefit of the local anesthetic prior to commencing the surgical procedure. The site is cleaned again with betadine. The surgeon then cleans their hands

again and puts on sterile gloves. The site should then be allowed to dry before surrounding the operative site with sterile towels or drapes.

Step 9: Surgical procedure

The surgical procedure commences by using a scalpel, blade size 15, where the skin at the center of the site is stretched and a 10-12 mm incision approximately 1-2 mm deep is created. This initial incision will simply be partially through the skin and so the blade is then reversed, and a firm incision is made approximately 5-10 mm deep while the reverse blade is used to cut completely through the skin along the 10-12 mm incision line.

Note: The following part of the procedure is described for a right-handed surgeon.

Step 10: The surgeon uses their left hand to lift the subcutaneous tissues to the left of the 10 mm incision and uses a pair of disposable sterile forceps in their right hand to break through into the subcutaneous tissues that they have exposed with their left hand. The procedure is then repeated with the opposite hands when inserting the same forceps into the subcutaneous tissue on the participant's right side of the abdomen.

Pick up the applicator device and remove the applicators cover on the front of the instrument, ensuring that the syringe applicator is held correctly (Figure 7.3). Do not open the back end of the device as there is a risk of tablets escaping if this is opened prematurely.

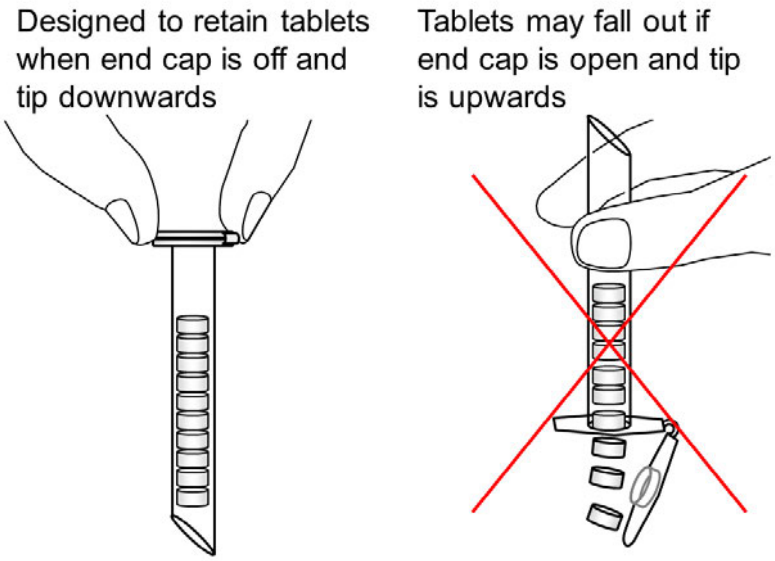

Figure 7.3: Correct holding of syringe applicator

Note: The following description applies to a right-handed surgeon inserting the first implant into the participant's left side of the abdomen.

Step 11: The surgeon uses their left hand to lift the subcutaneous tissues of the abdominal wall just 1-2cm to the left of the incision. The bevel of the applicator should be facing upwards and the applicator is inserted carefully into the incision, ensuring that the applicator is placed under the adipose tissue but above the muscle sheath (Figure 7.4) until firm resistance from the subcutaneous tissues is felt.

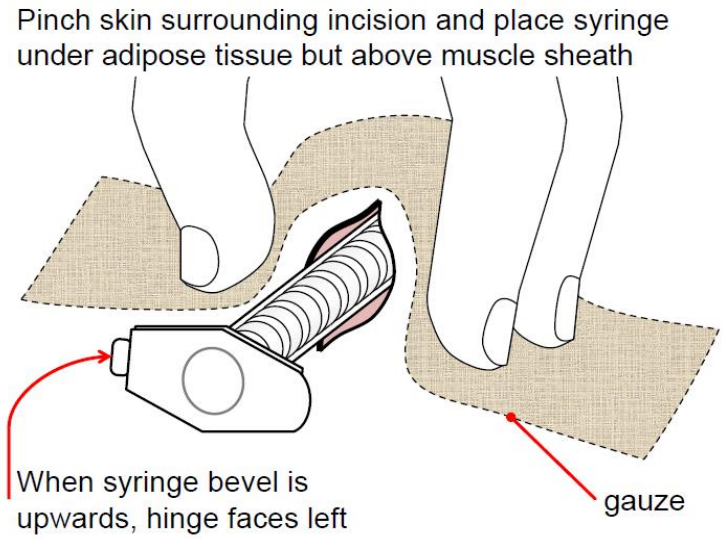

Figure 7.4: Syringe applicator insertion

Step 12: Using the surgeons left hand it is then possible to push the subcutaneous tissues against the applicator until the applicator advances for 5-10 mm. The surgeon's left hand is then moved 5-10 mm away from the incision and lifts up the adjacent subcutaneous tissues. The procedure of then pushing the subcutaneous tissues firmly against the bevel of the applicator will allow another 10 mm of movement along the marked central line. This procedure is repeated a series of times until the applicator is fully inserted and sitting just above the sheath with a significant covering of subcutaneous tissues above the applicator. The applicator's trocar can then be picked up in the surgeon's right hand and the opening of the applicator's rear cap can then occur providing the participant is leaning a little to the left so that there is no risk of tablets being lost from the applicator. The trocar is then inserted firmly (Figure 7.5) so that the tablets are slowly pushed forward while the applicator is slowly withdrawn.

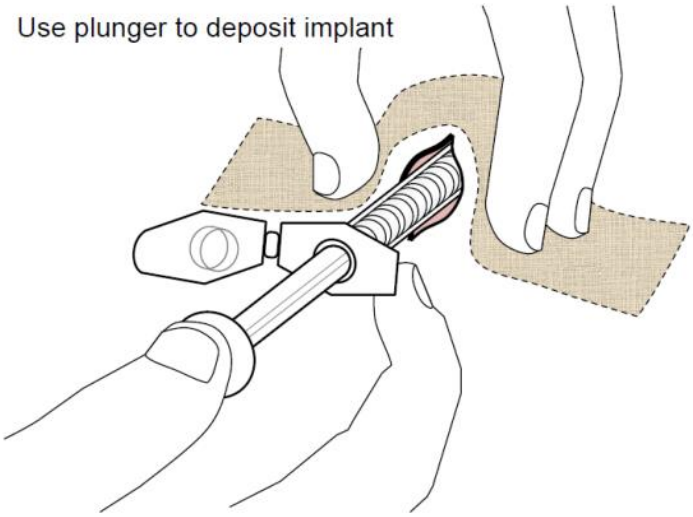

Figure 7.5: Insertion of OLANI using Syringe plunger

If this is carried out carefully then tablets will be in a line rather than pushed into one ball (Figure 7.6). It is preferable that the tablets be pushed gently in a line to ensure correct placement.

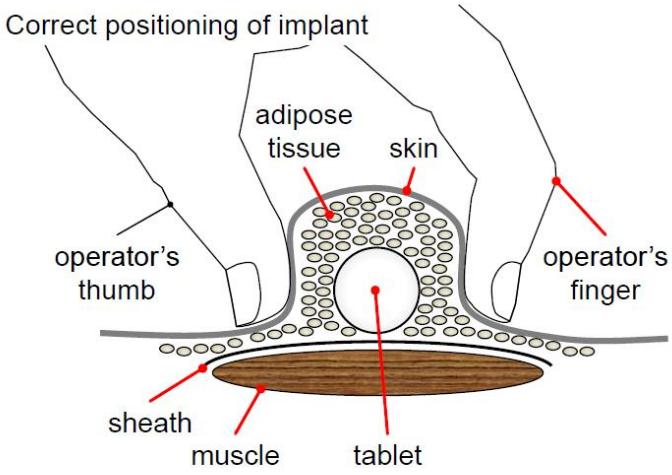

Figure 7.6: Correct positioning of OLANI

Step 13: The procedure is then repeated through the same incision using a second applicator syringe to position the OLANI tablets on the other side of the abdomen. The site of each OLANI's will be recorded on the CRF.

Step 14: Closure of the incision

It is important that closure be carried out in two layers. The first involves closure of the subcutaneous tissues. This should usually be carried with an absorbable suture. We recommend a 3-0 monocryl or biosyn deep dermal suture layer. The second layer of closure requires the skin to be closed using a cyanoacrylate medical glue. In the practical care of those with addictions the glue has proved to be very acceptable as

participants who fail to return for routine assessment following their procedures do not have the risk of a stitch abscess. Following the application of glue, steri-strips are applied, and the wound is covered with a dressing.

7.1.1.4 Wound Site/Implant Site Assessment

7.1.1.4.1 SURC Clinic (Initial 48 hours)

Wound Site/Implant Site Assessment will be carried out by the study PI Dr. Bisaga (trained in the evaluation by the study surgeon Dr. Rohde), using the Implant Site Evaluation Form (ISEF). The wound/implant site will be assessed at 24 ±2 hours and 48 hours ±2 hours after the procedure and more frequently if clinical indicated. Any concerns that are identified by the ISEF will be referred to the study surgeon for evaluation and treatment as per 7.6.2.

7.1.1.4.2 Clinilabs Clinic (Post 48 hours)

Wound Site/Implant Site Assessment will be carried out by a research nurse (trained by the study surgeon Dr. Rohde), using the ISEF as per the protocol time points outlined in Table 7-1. Any concerns that are identified by the ISEF will be initially referred to the Clinilabs doctor for evaluation and treatment as per 7.6.2. The Clinilabs doctor will consult with the study surgeon if required.

If there are any concerns to the wound/implant site by the participants outside of regular study visits, they will be asked to come to the Clinilabs clinic for evaluation as above. All evaluations will be documented using the ISEF.

Note: As appropriate, participants may be seen for follow-up visits at the SURC clinic (i.e. if clinically indicated or if traveling to the Clinilabs clinic presents a hardship to a participant).

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 Clinical Laboratory Evaluations

Samples will be collected and sent for analysis to Lab Corp.

For the following test, 4.5 mL of blood will be collected in 1 tube (lavender top EDTA tube):

- *[FBC] Full Blood Count: RBC, WBC, Hematocrit, Hemoglobin, Platelet Count, Eosinophils, Basophils, Monocytes, Neutrophils, Lymphocytes, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Hemoglobin (MCH), Reticulocytes, Red cell distribution width (RDW), immature granulocytes*

For the following tests, 5 mL of blood will be collected in 1 tube (red/grey mottled top gel barrier SST tube):

- ***[FCP] Full Chemistry Panel with Liver Function Tests:*** *Glucose, Uric Acid, Blood Urea Nitrogen (BUN), Creatinine, Sodium, Potassium, Chloride, Calcium , Phosphorus, Protein Total, Albumin, Globulin, Albumin/Globulin A/G Ratio, Bilirubin (total), Bilirubin (direct), Bilirubin (indirect), Alkaline Phosphatase, Lactate Dehydrogenase (LDH) , AST (SGOT), ALT (SGPT), GGT, Iron, Total Cholesterol, Triglycerides, HDL Cholesterol, LDL Cholesterol (calculated), Magnesium, CO2, CPK, Amylase , Lipase*

For the following tests, 5 mL of blood will be collected in 1 tube (lavender top EDTA tube):

- *Hepatitis A IGG*
- *Hepatitis B Serology*
- *Hepatitis C Serology*

For the following test, 5 mL of blood will be collected in 1 tube (red/grey mottled top gel barrier SST tube):

- *HIV Serology*

For the following tests, a sample of urine is collected:

- *UA (Urinalysis) including urine color, appearance, bilirubin, urobilinogen, WBC esterase and a microscopic examination (WBC, RBC, epithelial cells, mucus threads, bacteria)*
- *LEU (Leucocytes), NIT (Nitrite), PRO (Protein), pH, BLD (Blood), SG (Specific Gravity), KET (Ketones), GLU (Glucose)*
- *[UDS] Full drug screen including morphine, oxycodone, methadone, cocaine, amphetamines, hydromorphone, hydrocodone, codeine, methamphetamines, thc, benzodiazepines, fentanyl and buprenorphine assay.*

Pregnancy test: For all female participants, a blood test is done initially, with urine tests done monthly afterwards. A blood test will be used to confirm a positive urine result.

7.2.2 Other Assays or Procedures

7.2.2.1 Naltrexone Blood Level Assay

9 mL of whole blood will be collected into 10cc Na Heparin (green top) tubes (see Section 7.2.4.1 for more details regarding the procedure).

7.2.3 Total amount of Blood to be collected

The amount of blood drawn for the study is:

- HIV and Hepatitis screening = 10 mL.
- FCP and FBC = 180.5 mL (18 x 9.5 mL)
- Pregnancy testing (Female participants only) = 4 mL (during the trial, a blood test will be used to confirm a positive urine result)
- Total blood samples for naltrexone / naltrexol = 288 mL (32 x 9 mL)
- There is also the potential for further bloods to be taken on any un-scheduled visit for PK bloods (10 mL) and follow-up visit for outstanding AEs (FCP and FBC 9.5 mL) post end of trial.

Note: that the total blood samples for naltrexone / naltrexol have been calculated for the worst case of participants going out to Day 540. In the event that a participant registers two consecutive monthly naltrexone blood levels recorded at <0.1 ng/mL, then the participant will be withdrawn from the study and the blood collection will be reduced by 10 mL for every monthly time point not required.

7.2.4 Specimen Preparation, Handling and Storage

7.2.4.1 Naltrexone Blood Level Assay

All naltrexone blood samples will be collected in 1 x 10 mL Na Heparin tubes (9 mL) and stored in the refrigerator at 0-4°C until specimen preparation. Specimen preparation will be carried out within 30 minutes of collection. This will involve centrifugation of the blood sample in an ambient centrifuge for 15 min at 2,000 rpm within 30 minutes of collection to enable plasma separation. **The plasma will be extracted and transferred into two 2 mL cryovials (2 aliquots total). Cryovials with aliquot will be stored in a freezer at no warmer than -70°C until shipment.**

All plasma samples up to 48 hours will be collected, processed and stored at NYSPI. All plasma samples scheduled after 48 hours will be collected, processed and stored at Clinilabs. When batches of greater than 50 samples are available these can then be shipped on dry ice to the PK analysis laboratory for free (unconjugated) naltrexone and free (unconjugated) 6-β-naltrexol analysis. Backup samples will remain stored at Clinilabs and NYSPI for the duration of the trial.

7.2.5 Specimen Shipment

Plasma will be stored for batch shipment to the PK analysis laboratory for analysis. Storage of samples at no warmer than -70°C will be done at Clinilabs and NYSPI. Shipment of samples to the PK laboratory will be done under dry ice.

7.3 STUDY SCHEDULE

7.3.1 Screening Visit 1

Participant shall be screened for inclusion and exclusion criteria and overall suitability for the study.

- Obtain informed consent for screening.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical and psychiatric examinations, including Patient Health Questionnaire (PHQ) and Beck Depression Inventory (BDI-II), MINI-International Neuropsychiatric Interview (MINI), needed to determine eligibility based on inclusion/exclusion criteria.
- Concomitant medication review.
- Physical (Record BMI) and mental status exam.
- Vital signs.
- A 12-lead ECG will be conducted for each measurement, the subject should be resting during the 10 minutes prior to the measurement time point and in a semi-recumbent or supine position at the measurement timepoint. RR, PR, QRS, QT, QTcF and QTcB will be collected. ECGs will be measured with equipment calibrated as per site standard operating procedures and will be assessed by a qualified clinician.
- C-SSRS-Lifetime.
- Breathalyzer Assessment

7.3.2 Screening Visit 2

Review of inclusion and exclusion criteria and overall suitability for the study.

- Collect blood for FBC, FCP.
- Collect urine for UA, and UDS.
- Collect blood for Hepatitis and HIV tests.
- Collect blood for baseline naltrexone and 6-β-naltrexol measurement.
- Collect blood for pregnancy test in female participants.
- Self-reported substance use (using the Recent Drug Use-Baseline [RDU]).
- Concomitant medication review.
- AE Monitoring.

7.3.3 Recruitment Visit

At the Recruitment visit the following will take place;

- Review of screening assessments and study inclusion exclusion criteria. All screening assessments must be collected within 30 days prior to the Recruitment visit,
- Obtain informed consent for IP administration.
- Concomitant medication review.
- AE Monitoring.
- Breathalyzer Assessment

7.3.4 Day -1 to Day 2 ('Admission' Days)

7.3.4.1 Admission Day -1

Participants will be admitted to the SURC clinic at the NYSPI where they will complete the PHQ, BDI-II, Substance Use assessment, urine drug screen, concomitant medication review and AE monitoring. Each participant will then undergo the NCT to confirm opiate naivety based on COWS score.

7.3.4.2 Admission Day 0

Participants will be scheduled for administration of the OLANI as outlined in section 7.1.1.3. After a review of concomitant medications and vital signs are obtained, participants will be fitted with the iv cannula to aid in the collection of blood sample for the first 48 hours. There shall be no use of heparin to keep the cannula clear as this may affect the blood analysis of naltrexone and 6-β-naltrexol. Processing and storage of blood samples shall be done as per section 7.2.4.1.

The recorded dose time (0 hour) will be the time at which the procedure will be completed. Naltrexone blood samples (see section 7.2.4.1) will be collected at the following time points: 3 hours ±60 min, 6 hours ±60 min, and 12 hours ±60 min. The actual time of each PK sample collection shall be recorded.

Participants will also be monitored for AEs.

7.3.4.3 Admission Day 1

Naltrexone blood samples (see section 7.2.4.1) will be collected at 24 hours ±2 hours after the OLANI procedure. The actual time of each PK sample collection shall be recorded.

Participants will also be monitored for AEs, have a review of concomitant medications and have a Wound Site/ Implant Site Assessment as per 7.1.1.4.

At this time, participants will have the option of remaining an inpatient or being discharged from the SURC clinic and returning for the 48-hour observation (Admission Day 2).

7.3.4.4 Admission Day 2

Naltrexone blood samples (see section 7.2.4.1) will be collected at 48hours ±2 hours after the OLANI procedure. The actual time of each PK sample collection shall be recorded.

Participants will also be monitored for AEs, have a review of concomitant medications and have a Wound Site/ Implant Site Assessment as per 7.1.1.4.

Remaining inpatient participants will be discharged from the SURC clinic.

All participants will be provided with a timetable for their follow-up visits, which will be carried out at the Clinilabs clinic.

7.3.5 Follow-Up Day 4 to 540

Participants will be instructed to attend the Clinilabs clinic to continue study procedures on an outpatient basis as per the protocol time points outlined in Table 7-1. There are allowable variations in actual day of collection as long as the variation is recorded. The following will be collected at all time points: Concomitant medical review, PK blood collection, AE monitoring, vital signs (Blood pressure, heart rate, respiratory rate, and oral body temperature) and a Wound Site/Implant Site assessment (see section 7.1.1.4).

The following will also be collected on day 28 and then monthly as outlined in Table 7-1, PHQ & BDI-II, C-SSRS, FBC, FCP, UA, Pregnancy test (initial with urine with serum testing used to confirm positive results), substance use reporting (self-report using the Quantitative Substance use Inventory) and UDS.

Note: As appropriate, participants may be seen for follow-up visits at the SURC clinic (i.e. if clinically indicated or if traveling to the Clinilabs clinic presents a hardship to a participant).

SARS-CoV-2 Note: This study is being conducted in New York, NY; a location heavily impacted by the COVID-19 pandemic. Therefore, for the safety of study participants, the IRB requested on 21 April 2020 that in-persons study visits be stopped and replaced with telephone or video visits. Thus, where in-person study visits are not possible, safety will be monitored remotely. This change means that for some participants, certain procedures (e.g. PK blood draws), may be missed during the time of the public health emergency. Table 7-1 has been updated to indicate which procedures will be captured by telephone/video visits and which procedures may be missed due to COVID-19. In case there are safety concerns that need in-person evaluation to determine best course of action, such as new-onset implant site-reaction or site drainage, then an in-person visit at the clinic will be conducted.

This change was implemented on 27 April 2020 and all missed visits/procedures are being tracked. In person visit will resume immediately when deemed safe and appropriate by the IRB.

7.3.6 Final Study Visit

All participants will be required to attend the SURC clinic for a final visit with a study PI as outlined in Table 7-1. The final visit will be scheduled as soon as possible after two non-detectable PK samples have been obtained, or after Day 540 visit has occurred.

7.3.7 Early Termination Visit

Any participants that are withdrawn will be required to attend the SURC clinic for an early termination /withdrawal visit as outlined in Table 7-1. Participants will be advised of their options as outlined in in section 5.4.2.

A follow-up visit may be conducted 30 days after the last scheduled on-study visit and is required only if a participant has ongoing AEs or laboratory abnormalities at the last on-study visit. An in-clinic follow-up visit must be conducted 30 days after the last scheduled on-study visit for an AE requiring laboratory testing for participants with the following conditions at the last on-study visit: ongoing AEs, SAEs regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the participant. For in-clinic follow-up visits, assessments performed should reflect what is considered medically necessary to assess the event(s).

7.3.8 Unscheduled Visit

It is anticipated that some participants may miss or be delayed to some of their appointments. Every effort will be made to obtain blood samples at the scheduled dates, but blood samples will be accepted if they are taken late, with allowances made in the statistical analysis for this. Participants who miss appointments will be contacted by phone to encourage them to return for as many appointments as possible. However, some dropouts are also anticipated so additional participants will be recruited to get the correct totals for analysis.

Participants will be asked to complete the following; vital signs, concomitant medication review, wound site/implant site assessment and AE monitoring (see Table 7-1). Additional assessments performed at Unscheduled visits are at the discretion of a study physician.

7.3.9 PK Follow-up Visit

PK follow-up visit may be conducted 30 days after the last monthly PK visit 540 days, if the participant has detectable naltrexone plasma levels. Follow-up visits will continue until two consecutive monthly naltrexone blood levels recorded at <0.1 ng/mL are received from the lab and recorded. If the latest PK levels are pending, participants will continue to make follow-up visits (see Table 7-1).

7.3.10 AE Follow-up Visit

A follow-up visit will be conducted 30 days after the last scheduled on-study visit. This visit is required only if a participant has ongoing AEs or laboratory abnormalities at the last on-study visit (see Table 7-1). An in-clinic follow-up visit must be conducted 30 days after the last scheduled on-study visit for an AE requiring laboratory testing for participants with the following conditions at the last on-study visit: ongoing AEs, SAEs regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the participant. For in-clinic follow-up visits, assessments performed should reflect what is considered medically necessary to assess the event(s). All other participants that will have additional questions or concerns about the fate of the implant will also be encouraged to come for a follow-up meeting with a study physician.

7.3.11 Assessment Time Point Tables

Table 7-1: Assessment Time Points

	Screening Visit 1[10]	Screening Visit 2[10,11]	Recruitment Visit [10]	Admission Day -1[10]	Admission Day 0[12]	Admission Day 1 & 2[10]	Day 4[13] (±1 day)	Day 8[13] (±2 days)	Day 14, 21, 35, 42 & 49[13] (±3 days)	Day 28 & 56[13] (±3 days)	Monthly PK Visit[7,13,14] (±10 days)	Final Visit[10]	Early Termination / Withdrawal[10]	Un-scheduled Visit[13,14,15]	PK Follow-up[8,13]	AE Follow-up[9,13,14]
Inclusion/Exclusion Criteria [1]	X	X	X													
Informed Consent	X															
IP Informed Consent			X													
Demography	X															
Medical History	X															
MINI-International Neuropsychiatric Interview (MINI)	X															
Physical Exam	X											X		X		
12 Lead ECG	X											X		X		
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breathalyzer Assessment	X		X											X		
PHQ, BDI-II	X			X						X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale -C-SSRS1 (Lifetime) [2]	X															
Columbia Suicide Severity Rating Scale (Since last visit) [2]										X	X	X	X	X	X	
Safety Labs (Chemistry, Hematology, Urinalysis)		X								X	X	X	X	X	X	X
PK Blood Collection		X[3]			X[5]	X[5]	X	X	X	X	X	X	X	X	X	
Pregnancy Test		X[4]								X	X	X		X	X	
Viral Serology		X														

	Screening Visit 1[10]	Screening Visit 2[10,11]	Recruitment Visit [10]	Admission Day -1[10]	Admission Day 0[12]	Admission Day 1 & 2[10]	Day 4[13] (±1 day)	Day 8[13] (±2 days)	Day 14, 21, 35, 42 & 49[13] (±3 days)	Day 28 & 56[13] (±3 days)	Monthly PK Visit[7,13,14] (±10 days)	Final Visit[10]	Early Termination / Withdrawal[10]	Un-scheduled Visit[13,14,15]	PK Follow-up[8,13]	AE Follow-up[9,13,14]
AE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen		X		X						X	X	X			X	
Recent Drug Use-Baseline (RDU)		X														
Quantitative Substance Use Inventory				X						X	X	X		X	X	
Naloxone Challenge Test				X												
COWS Baseline, 10 Minutes, 20 Minutes, 30 Minutes				X												
Subcutaneous Implant (Dosing) EX					X											
Vital Signs (Height, Weight, BMI)	X															
Vital Signs with weight[16]					X		X	X	X	X	X	X	X	X	X	X
Wound Site/ Implant Site Assessment						X[6]	X	X	X	X	X	X	X	X	X	

1. **Inclusion/exclusion criteria** will only be reviewed at Screening Visit 2 and the Recruitment Visit.
2. **C-SSRS** will be used to assess suicidal risk. Lifetime risk will be assessed at screening visit 1, with subsequent visits assessing risk since last visit (SLV).
3. A blood sample will be taken for NTX & 6BN at Screening Visit 2.
4. **Pregnancy testing** will be conducted on all females of child bearing potential on serum at screening, subsequent testing will be carried out on urine samples with serum testing used to confirm positive urine results as per section 7.2.1.
5. **Initial 48 hours PK Sampling** - Blood samples will be collected at the following time points: Baseline screening visit, 3 hour ±60 min, 6 hour ±60 min, 12 hour ±60 min, 24 hour ±2 hours and 48 hour ±2 hours after the implant procedure. The actual time of each PK sample collection should be recorded.
6. **Wound site/implant site assessment** for day 1 (24h) and day 2 (48) will take place within ±2hours.
7. **Monthly PK visit** - Blood samples will be collected at the following time points: Day 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510 & 540.
8. **PK follow-up visit** may be conducted 30 days after the last monthly PK visit 540 days, if the participant has detectable naltrexone plasma levels. Follow-up visits will continue until two consecutive undetectable naltrexone plasma levels (defined as naltrexone blood levels of <0.1 ng/mL) are recorded.
9. **AE follow-up visit** may be conducted 30 days after the final study visit and is required only if a participant has ongoing AEs or laboratory abnormalities. A follow-up visit must be conducted for an AE requiring laboratory testing for participants with the following conditions: ongoing AEs, SAEs regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the participant.
10. **Institution** = SURC clinic for all visits up to and including the initial 48 hours, and Final Visit or Early Termination Visit (as applicable). Additional follow up visits may also occur at the SURC clinic when appropriate. Further, a **Discharge CRF** is to be completed at the time of participant discharge (i.e. approximately 24 or 48 hours after the procedure).
11. For analysis purposes, **Baseline** is defined as Screening Visit 2. However, the following measures from Screening Visit 1 should also be included in the Baseline analysis: PHQ, BDI-II, CSSRS Lifetime, and Vital Signs.

12. **Satellite Location 1** = Columbia University Medical Center (CUMC), 177 Fort Washington Ave., New York, NY 10032, USA
13. **Satellite Location 2** = Clinilabs, 423 West 55th St, New York, 10019 for all visits after the initial 48-hour time-point
14. **Changes Due to COVID-19:** During the public health emergency, some of the monthly follow-up visits may occur by telephone/video only. The following safety assessments will occur during these remote study visits: concomitant medication review, PHQ (BDI-II), C-SSRS1 (since last visit), AE monitoring, Qualitative Substance Use Inventory and wound site/implant site assessment (self-reported) done via video link, if possible. Conversely, the following assessments/procedures may be missed because of having remote study visits: safety labs, PK blood collection, pregnancy test, urine drug screen, vital signs/weight.
15. **Unscheduled Visits:** Vital signs, concomitant medication review, wound site/implant site assessment and AE monitoring are to occur at all Unscheduled Visits. Additional assessments performed are at the discretion of a study physician.
16. **Vital Signs:** Blood pressure, heart rate, respiratory rate, and oral body temperature will be measured after the subject has been in a seated position for at least 5 minutes.
    Note: After a subject's last visit, the **Disposition CRF** must be completed.

7.4 CONCOMITANT MEDICATIONS, TREATMENTS AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 PROHIBITED MEDICATIONS, TREATMENTS AND PROCEDURES

The medications and substances listed below are prohibited for the specified time periods:

- **Buprenorphine**, either as part of a maintenance program or any illicit/non prescribed is prohibited for the duration of the study.
- **Methadone** is prohibited at least 14 days prior to Day 0 and for the duration of the Study.
- All other **opioids** are prohibited for the duration of the study unless approved by the PI or study clinician (see section 7.7)
- **Oral naltrexone** is prohibited for at least 30 days prior to Day 0 and for the duration of the study
- **Other forms of extended release naltrexone (e.g. Vivitrol)** is prohibited for at least 24 months prior to Day 0 and for the duration of the study

7.6 PROPHYLACTIC MEDICATIONS, TREATMENTS AND PROCEDURES

7.6.1 Prophylactic Medications

One dose of IV antibiotic within 30 minutes of the surgical procedure is given as part of the implantation procedure (7.1.1.3):

2g cefazolin IV If allergic to cephalosporins or penicillin, then alternative is 600 mg clindamycin

7.6.2 Management of Infection/ Inflammatory Responses to the Wound/Implant Site

All Participants will have their wound site / implant site regularly assessed as per 7.1.1.4 for signs of infection and/or inflammatory reactions. Particular attention shall be paid during follow-up visits at day 4, 8, 14 and 21 (as per 7.3.11) for signs of infection to the wound site or early signs of an inflammatory reaction to the implant. Symptoms and signs relating to redness, excessive itchiness and/or increasing pain at the implant or wound site may be attributed to the inflammatory response. Symptoms relating to edema, spreading cellulitis, fever and general feeling of malaise are likely to be attributed to infection of the implant or wound site. Inflammatory reactions tend to occur much more frequently than infections. Treatment for inflammatory reactions or infections should be performed as specified below.

Infection treatment protocol

Infections present in participants as spreading cellulitis with other clinical indicators such as fever or general malaise. Spreading cellulitis involves redness of the skin which may extend several centimetres around the wound and extend over the area of the implant. Participants

with spreading cellulitis should be treated immediately with antibiotics (e.g., cephalexin) with physical exam and/or laboratory results used to monitor treatment response. If the infection does not resolve with oral antibiotics, a course of IV antibiotics may be necessary.

Inflammatory responses without an infection

Signs of redness, swelling, tenderness, itchiness or pain as identified from the ISEF after day 14 without the presence of fever or general feeling of malaise, suggests the onset of a mild inflammatory response to the implant only and the treatment regime described below (level 1 to level 4) should be implemented.

Level 1 treatment (25 mg prednisone)

Participants should be prescribed prednisone at 25 mg daily for the first 7 days followed by a tapered dose of 12.5 mg for an additional 14-days. The participant should be evaluated 3 days after the start of prednisone. If symptoms have not improved after 3 days then participants shall progress to Level 2 treatment.

Level 2 treatment (50 mg prednisone)

If Level 1 treatment is not resolving the pain and swelling, the dose of prednisone shall be increased to 50 mg per day. The participant should be re-assessed after 3 days. If after 3 days symptoms are improving, then the participant should return to the Level 1 treatment protocol. If after 3 days the symptoms have not improved, then participant shall progress to Level 3 treatment protocol.

Level 3 treatment (betamethasone and fluid assessment)

Participants who have failed to respond to Level 2 treatment, shall stop their oral prednisone and be given an injection of betamethasone, with 1 mL diluted in saline or local anesthetic (1% lidocaine, 3mL) injected around the implant site where inflammation is occurring in the absence of fluid build-up.

If there is fluid present prior to the betamethasone injection, the fluid must be aspirated. To achieve aspiration of the fluid, a needle with a wide bore is required to aspirate what can be quite thick viscous pus-like fluid. The aim of the drainage is to a) relieve tension and b) remove the fluid build-up. It is therefore important to lavage the fluid space until a CLEAR ASPIRATE is obtained. Lavage the space with normal saline or Hartman's solution. This normally requires multiple lavages, usually about 10mL each time. The final drainage(s) is/are performed without suction, to avoid dislodging/damaging the implant. Drainage and lavage are followed with a brief course of oral prophylactic antibiotic.

Where there are two implant sites, a second injection will be required for the second site (if it is also affected by the inflammatory process). The participants should rest for 30 min following the procedure to maximize the chance of the betamethasone remaining in place.

Note: betamethasone should not be substituted for any other steroidal injection with an alcohol base carrier as this will affect the implant composition.

After 3 days of review, if inflammatory symptoms have fully resolved and there are no signs of an infection then no further treatment is required and participant is observed only. If inflammatory symptoms have improved significantly but not fully resolved then participant should return to Level 1 treatment protocols. If inflammatory symptoms have slightly improved but not fully resolved a second round of betamethasone injections can be commenced.

Level 4 treatment (removal of implants)

In participants that do not respond adequately to the treatment regime, the implant(s) should be surgically removed. This can be achieved by a surgical incision over the implant site and should be done by the study surgeon when possible.

Inflammatory response with secondary infection

Some participants will develop fluid around their implant as an inflammatory response to the implant. The build-up of fluid causes pressure and symptoms such as pain which can result in the fluid tracking through the line of least resistance and be expelled through the initial surgical incision. This can lead to the wound opening and the risk of secondary infection, as well as implant expulsion. If the implant and wound site is treated according to level 1 to level 4 protocols for inflammatory responses then the risk of this occurring is reduced.

Where the fluid build-up is great enough to cause rupture and discharge, the open wound is at risk of secondary infections. This clinical situation is actually primarily due to an inflammatory response to the implant with a secondary outcome of an infection as a result of an open wound. In such cases, the inflammatory response should be treated as per the inflammatory response protocol starting at level 3 with the addition of oral antibiotics. Treatment with appropriate oral antibiotics should be initiated on the diagnosis and modified if necessary based upon results of culture swabs from the surface of the wound.

Most of the wounds close within a few days of the treatment resulting in the process settling as the fluid drainage no longer keeps the wound open. If the infection is not resolving after 3 days of oral antibiotics, then IV antibiotics should be introduced. In participants that do not respond adequately to the treatment regime, the implant(s) should be surgically removed. This can be achieved by a surgical incision over the implant site and should be done by the study surgeon when possible. Antibiotics shall be continued after surgical removal to treat the remaining infection until all symptoms have resolved.

7.7 RESCUE MEDICATIONS, TREATMENTS AND PROCEDURES

As naltrexone acts as an opioid blocker participants requiring pain relief during the study period will be offered appropriate pain medications e.g. tramadol, reginal blocks or partial opioid agonist such as buprenorphine.

7.8 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

N/A

7.9 REIMBURSEMENT COSTS

Participants will receive reimbursement as follows.

- $50 for each of the two screening visit (2 visits)
- $50 for the consent visit (1 visit)
- $400 for Day -1 to Day 2, the Admission Days (either 1 or 2 visits)
- $50 for each scheduled outpatient visit (25 visits). Participants will receive an additional incremental bonus of $10 for each subsequent visit attended (Visit 1: $50, visit 2: $50+$10, Visit 3: $50+$20, Visit 4: $50 +$30 …). In case the scheduled visit is missed the value of the bonus is reset to the starting value of $10. This schedule is designed to reinforce adherence to all study safety assessments. Participants will not be penalized for missed visits during the COVID-19 pandemic as long as they attend telephone/video visits in place of the scheduled clinic visit.
- Travel reimbursements – in addition to the amounts specified above, participants will receive $20 for travel at each visit, and up to $50 in travel if participants provide receipts.

The total amount of reimbursement should a participant attend every scheduled visit is $4,800 plus a maximum of $1500 in travel reimbursements depending on provided receipts.

If a participant is required to return for further PK or AE follow-up visits, then they will receive $50 plus the incremental bonus, plus $20 for travel, or up to $50 in travel if participants provide receipts.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety will be assessed on the basis of:

- the incidence of death
- the incidence of SAEs
- the incidence AEs leading to discontinuation
- the incidence common AEs
- the incidence complications of insertion
- the incidence implantation site reactions
- laboratory abnormalities indicating hepatic problems (absolute values and changes over time)

8.1.1 Definition of Adverse Events (AE)

AEs will be identified from the telephone interviews, face to face visits or from the CRF. They will be recorded on an AE form.

Definitions

An AE is any untoward medical occurrence in a clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product. An adverse event is any adverse change (developing or worsening) from the patient's pre-treatment condition, including concurrent illness.

The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

8.1.2 Definition of Serious Adverse Events (SAE)

A SAE is any adverse experience occurring during the study period that:

- results in death;
- is life-threatening;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity; or
- results in congenital anomaly/birth defect.

A *life-threatening* AE is one that actually places the participant at immediate risk of death. A participant's reaction is not classified as life-threatening simply because more severe manifestations of the same adverse reaction can be fatal, e.g. mild airway obstruction is not life threatening but severe airway obstruction is.

Hospitalization includes any inpatient admission, any transfer within a hospital for the purpose of treatment (for example, transfer of a participant from a psychiatric unit to a general medical unit) and prolongation of admission. Prolongation of hospitalization is

defined as any extension of an inpatient hospitalization beyond the stay anticipated/ required in relation to the original reason for the initial admission, as determined by the investigator or treating physician.

Study coordinators will report any new SAEs to the PI, NYSPI IRB, DSMB and sponsor within 24 hours of first knowledge.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 Severity of Event

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Medication and Surgical Procedure

The clinician's assessment of an AE's relationship to the study medication (i.e. OLANI) or the surgical procedure is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

8.2.3.1 Adverse Drug Reactions Commonly Seen from Naltrexone (MIMS)

- *Difficulty sleeping*
- *Anxiety*
- *Nervousness*
- *Abdominal pain/cramps*
- *Nausea and/or vomiting*
- *Low energy*
- *Join and muscle pain*
- *Headache*
- *Loss of appetite*
- *Diarrhea*
- *Constipation*
- *Increased thirst*
- *Increased energy*
- *Depressive mood*
- *Irritability*
- *Dizziness*
- *Skin rash*
- *Delayed ejaculation*
- *Erectile dysfunction*
- *Reduced sexual desire*
- *Chills*

8.2.3.2 Adverse Events Commonly Seen Following Implantation procedure

- *Local inflammatory reaction; itchiness, redness, heat or swelling*
- *Wound site Infections*
- *Hematoma*

8.2.3.3 Adverse Events Rarely Seen Following Implantation procedure

- *Allergic reactions to suture material*
- *Implant removal for infections or allergic responses*
- *Implant removal for psychological reasons.*

8.2.3.4 Adverse Events Commonly Seen from Poly Lactide Polymer

- *Local inflammatory reaction; itchiness, redness, heat or swelling*

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

In the event of study discontinuation for any reason, any ongoing AEs will be followed until resolution, or in the event of removal of the OLANI for at least 4 weeks after the removal, until deemed stable by the PI, or until the participant is deemed by the PI to be lost to follow-up. If, in the opinion of the PI, it is necessary to monitor a participant beyond the safety follow-up visit, the follow-up period may be extended as necessary. In such instances, the sponsor and the PI will agree to an acceptable follow-up schedule. The PI must maintain a record of all participants who fail to complete the study. The reason for study discontinuation will be made on the appropriate CRF.

8.4 REPORTING PROCEDURES

8.4.1 Adverse Event Reporting

The sponsor will inform the investigator of any new information that may impact the conduct of the trial or have an impact on the ethical acceptability of the trial.

Investigator shall report all AE's on a monthly basis to sponsor and Data Safety Monitoring Board (DSMB) for review.

The sponsor will update the Investigator Brochure regularly with any new safety information relating to the drug.

8.4.2 Serious Adverse Event Reporting

All SAEs should be reported immediately to the sponsor, NYSPI IRB, FDA, DSMB except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as

not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers assigned to the trial participants rather than by the participants' names personal identification numbers, and/or addresses.

8.4.2.1 Management of SAE's

SAEs, as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE, whether or not related to study medication, will be reported to the NYSPI IRB, FDA & DSMB. The initial SAE report will be followed by submission of a completed SAE report to both institutions.

In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to SAE, the participant will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death. Outcome of SAEs will be reported to the NYSPI IRB, FDA & DSMB as soon as this information becomes available. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to the NYSPI IRB, FDA & DSMB.

8.4.3 Reporting of Pregnancy

Reporting of pregnancy will be to the treating physician, PI, NYSPI IRB and DSMB. After finding an incidental pregnancy the removal of the implant will be offered to the participant and the participant will decide how best to proceed in consultation with her obstetrician. The decision regarding the pregnancy will affect the decision whether or not to remove the implant at any point during the pregnancy. The risk of anesthesia differs during different times during pregnancy, however the risks of anesthesia and the risks of removal are both minimal.

8.5 STUDY HALTING RULES

8.5.1 Study Termination

The Sponsor reserves the right to close the investigational sites or terminate the study at any time. The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of an investigational site by the Sponsor or Investigator, or termination of a study by the Sponsor, may include but are not limited to:

- failure of the Investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines
- safety concerns
- inadequate recruitment of participants by the Investigator

Study termination will be reported to, NYSPI IRB, DSMB and FDA.

8.5.2 On-Site Audits

Representatives of the Sponsor's quality assurance department may visit the site to carry out an audit of the study in compliance with regulatory guidelines and the Sponsor's standard operating procedures. Audits and clinical trial monitoring will also be carried out by the CRO, Clinilabs during the trial period. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Participant privacy must, however, be respected. Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

8.6 DATA AND SAFETY MONITORING PLAN ADMINISTRATION

8.6.1 Responsibility for data and safety monitoring (DSM)

The study PI, Dr. Adam Bisaga, is required to be present for all DSMB meetings to provide reports for all accumulated data from the trial. The PI will also be primarily responsible for the implementation of any recommendations from the DSMB. The PI will be assisted in this duty by Dr. Edward Nunes, study Medical Monitor.

8.6.2 Frequency of DSM

Ongoing data and safety monitoring will be conducted weekly during research team meetings of the PI with the investigative team. Every three months, the PI and the medical monitor will review the number of participants enrolled, the number who completed the protocol, the number who dropped out of the protocol prior to completion (and reason why), any AEs, procedures for assuring participants privacy and confidentiality, and the quality and integrity of the data collected. Corrective action will be taken if needed. IRB study protocols and informed consent documents will be reviewed annually by the IRB. Reports of enrollment and retention and reporting of AEs are required with these renewals.

In addition, all studies involving human participants are periodically and systematically reviewed by the New York State Quality Assurance Staff. These procedures assure protocol compliance by conducting unannounced reviews of participants' research charts, comparing research charts to the IRB protocol. All SAEs will be reported to the FDA (as appropriate) and the DSMB in a timely fashion.

A separate DSMB (See 8.6.3 for details) will meet quarterly and within a week of any SAEs occurring. Ad hoc meetings may also occur if any study related issues arise during the course of the stud*y.*

8.6.3 DSMB Plan

The DSMB, will be chaired by Dr. Jonathan Stewart a Professor of Psychiatry at Columbia University College of Physicians and Surgeons and a senior expert in mood disorder pharmacotherapy. Three additional faculty members from the division will join the DSMB;

- Dr. Richard Foltin Ph.D, a senior researcher in the division, with more than 30 years of experience in the early phases of medication development for substance use disorders;
- Dr. Elias Dakwar, an opioid dependence treatment investigator in the division, and
- Dr. Arthur R. Williams, another research psychiatrist in the division.

Finally, Dr Jeffery Ascherman, Site Chief of the Division of Plastic Surgery and a Professor of Surgery at Columbia University Medical Center, will be on the DSMB and will provide surgical expertise.

The DSMB will meet before the study launch and quarterly afterwards to conduct initial and ongoing study review and review all AEs that occurred in the study. The DSMB will meet within a week of the occurrence of any SAE. For each SAE, the PI and covering physician will present a synopsis of how it occurred and how the incident was handled clinically so that DSMB can assess how the event was managed and if there are any recommendations that will maintain the high quality of the care that we provide to our research participants. Ad hoc meetings may also occur as needed to address study related issues.

All DSMB members will be asked to submit in writing any potential conflict of interest pertaining to the study. The DSMB will prepare a report in response to any SAE review meetings and will submit a DSM report annually. Reports will be submitted to the Sponsor and other authorities as appropriate. This report will include the following:

a) Brief description of the trial,
b) Baseline socio-demographic characteristics,
c) Retention and disposition of study participants,
d) Quality assurance issues,
e) Regulatory issues,
f) AEs,
g) SAEs
h) Efficacy.

9 CLINICAL MONITORING

This study may be participant to audit or inspection by representatives from the NYSPI IRB, DSMB or FDA.

Data from this study will be monitored by staff from the CRO, Clinilabs, for compliance with GCP principals. Monitoring will include review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring will include review of the investigator's site file and drug handling records. Clinilabs will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the participant authorizes Clinilabs staff direct access to their medical records and the study data.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

The statistical analysis will be collected in two stages, first at the interim stage (See 10.4.7), and second after the conclusion of all study procedures and database lock.

10.2 STATISTICAL HYPOTHESES

N/A

10.3 ANALYSIS DATASETS

The analysis will be performed based on Intention-to-Treat and Per-Protocol in all participants enrolled. Assessment of primary outcomes will be performed on participants who complete at least 75% of applicable time points.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 General Approach

Pharmacokinetic parameters will be expressed as a mean, standard deviation and co-efficient of variation for the group total. Similarly, the mean, standard deviation and co-efficient of variation plasma naltrexone and 6-beta-naltrexol will be calculated and tabulated for each time point.

10.4.2 Analysis of the Primary Endpoint

Participants who submitted at least 75% valid pharmacokinetic blood samples including 2 consecutive monthly naltrexone blood levels recorded at <0.1 ng/mL will be analyzed.

10.4.3 Analysis of the Secondary and Exploratory Endpoint(s)

Pharmacokinetic parameters (C_{max}, T_{max} and $AUC_{0-\infty}$, the period of time from insertion that naltrexone plasma concentrations remain above 1.33 ng/mL) will be calculated using a non-compartmental approach. Naltrexone plasma profiles will be plotted graphically for each individual and the study group (concentration-versus-time profile).

Use of opioids, cocaine, marijuana, and alcohol for each day of the study will be determined based on results of urine toxicology and self-report. Proportion of days with substance use for each participant will be summarized.

10.4.4 Safety Analyses

The frequency of AEs including wound site and inflammatory response rates will be recorded. Any SAEs, adverse drug reactions, and suspected unexpected serious AE will be collated for the combined group. Additionally, counts of the number of laboratory values that fall outside of the normal range will be used to assess safety.

10.4.5 Adherence and Retention Analyses

The percentage of participants that complete the desired number of follow up blood collection points will be calculated and presented with 95% confidence intervals.

10.4.6 Baseline Descriptive Statistics

Baseline characteristics will be calculated using mean, standard deviation, median, interquartile range, percentages and 95% confidence intervals (where appropriate).

10.4.7 Planned Interim Analyses

10.4.7.1 Safety Review

As per AE reporting, AEs will be collated and reviewed quarterly by the Safety Committee. This may include crude rates of type specific AEs; however, no formal interim analysis will be conducted.

10.4.7.2 Efficacy Review

An interim analysis will be carried out once at least 10 participants have completed their Day 180 PK blood time point. Participants, who submitted at least 14 of 19 valid blood samples (including the Day 180 sample) and safety data will be evaluated whether or not they met the MEC criteria (naltrexone blood level above 1.33 ng/mL). The analyzed interim data will be used in the planning and design of a bioequivalence/safety study of the OLANI against a reference extended release naltrexone product.

10.4.8 Additional Sub-Group Analyses

No sub-group analysis will be performed.

10.4.9 Multiple Comparison/ Multiplicity

No adjustment will be made for multiple comparisons.

10.4.10Tabulation of Individual Response Data

Individual pharmacokinetic and safety data will be tabulated for each time point and included in the appendices of the final study report.

10.4.11Exploratory Analyses

No exploratory analysis will be conducted.

10.5 SAMPLE SIZE

At the completion of the study it is desirable that a minimum of 10 participants complete a minimum of 75% blood collection time points, including 2 consecutive undetectable values (defined as naltrexone blood levels of <0.1 ng/mL).

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 Enrolment/ Randomization/ Masking Procedures

N/A as there is no blinding

10.6.2 Evaluation of Success of Blinding

N/A as there is no blinding

10.6.3 Breaking the Study Blind/Participant Code

N/A as there is no blinding

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Direct access to source data/documents will be provided to the sponsor, trial-related monitoring, audits, NYSPI IRB, and regulatory inspection(s).

12 QUALITY ASSURANCE AND QUALITY CONTROL

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP and the applicable regulatory requirements (e.g. Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP).

The investigational site will provide direct access to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the Sponsor, CRO (Clinilabs) and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 ETHICAL STANDARD

The study will be conducted in accordance with the guidelines and principles outlined in the International Conference on Harmonization - Standards of Good Clinical Practice[32] and the Declaration of Helsinki[33].Compliance with these standards ensures that the rights, safety and well-being of participants are consistent with the above principles.

13.2 INSTITUTIONAL REVIEW BOARD

The investigator will obtain NYSPI IRB approval for this study. Initial IRB approval as well as all materials approved by the IRB for this study, including the participant consent form and recruitment materials.

Annual Reports describing the study progress and all AEs will be provided to the NYSPI IRB, along with a final study report by the PI. A copy of this report will also be provided to the sponsor.

13.3 INFORMED CONSENT PROCESS

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

All study participants will be provided with a Participant Information Sheet (PIS) describing the study and providing sufficient information so that they are able to make an informed decision about their participation in the trial. Both the PIS and the Participant Informed Consent (PIC) form will be submitted with the research application for review and approval by the IRB.

13.3.2 Consent Procedures and Documentation

The investigator (or authorized designee) will ensure that the participant (or the participant's legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective participant will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the participant and must not include any language that waives the participant's legal rights. Prospective participants must also be informed of their right to withdraw consent without prejudice at any time during the study. If the participant chooses to participate, he/she must sign the ICF before any study-specific procedures are conducted.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

All data generated in this study will remain confidential. All information will be stored securely. participant information will only be disclosed to authorized individuals i.e. research personnel listed on the Delegation of Duties List who have signed a confidentiality agreement with the PI to undertake research related procedures.

All participant data will be de-identified by use of an alphanumeric study coding system.

Participant identification will be recorded on a Master Participants List held in-confidence by the PI in a locked cabinet separate to the de-identified data sheets.

Personal information recorded in study documentation or an electronic database will only be accessed by authorized study personnel. Personal computer access will be password protected and also limited to authorized study personnel.

Additionally, a Federal Certificate of Confidentiality will be obtained.

13.4.1 Research Use of Stored Human Samples, Specimens or Data

13.4.1.1 Naltrexone blood level

Samples collected up to and including the 48 hour time point will be prepared by study personnel from NYSPI for storage at -70ºC before shipment in batches to the PK analysis laboratory. Samples collected after the 48 hour time point will be processed by Clinilabs and stored until suitable batch sizes are available for shipment to the PK laboratory on dry ice. All samples will be analyzed for free (unconjugated) naltrexone and free (unconjugated) 6-β-naltrexol quantification. It is anticipated that samples will prepared and split into 2 aliquots, with 1 being used for analysis and 1 serving as a backup being stored de-identified in a -70°C freezer. Samples will be kept for 5 years after the completion of the trial, after which time they will be destroyed.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at NYSPI, as per local standard protocols.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

An electronic Case Report Form (eCRF) will be designed to record data required by the protocol and collected by the Investigator. An eCRF will be completed for each participant.

A confidential list of participant names, contact details, and screening numbers will be kept by the the Clinilabs and SURC clinics. eCRF data removed from the study site will be identified by the screening number and will not contain participant names or contact details.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

14.2 STUDY RECORDS RETENTION

Retention and storage of essential clinical study documents (e.g. worksheets, drug accountability forms, and other administrative documentation) shall be governed by the terms and conditions of NYSPI.

- Ten years after discontinuation of the study, or
- Two years following the date a marketing application is approved for the study drug for the indication for which it is being investigated pursuant to the study, or
- If no application is to be filed or if the application is not approved for such indication, until 2 years after the date the study is terminated.

Participants' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, SOP's and GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff at the SURC clinic, CUMC, or Clinilabs clinic. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The PI should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from NYSPI IRB, except where necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

If the PI implements a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial participants, without prior approval/favorable opinion from NYSPI IRB. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- To NYSPI IRB for review and approval/favorable opinion,
- To the sponsor for agreement and, if required,
- To the regulatory authority.

The PI, or person designated by the PI, should document and explain any deviation from the approved protocol.

14.4 PUBLICATION AND DATA SHARING POLICY

The data will be entered and analyzed by a PI, Clinilabs, and additional study personnel from NYS Psychiatric Institute. A Clinical Study Report will be issued which may form the basis of a manuscript intended for publication. Any publications arising from this study will be published by a process of peer review.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study leadership will be composed of the PI, the Responsible Clinician, Sponsor Representative, and site representative (See section 1)

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the IRB has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 REVISION HISTORY

Date	Version Number	Reason for Revision
02 November 2017	0.1	New document
24 November 2017	0.2	Internal revisions draft
18 January 2018	0.3	Internal revisions draft
26 January 2018	0.4	Internal revisions draft
07 February 2018	0.5	Original Protocol submitted to FDA
19 March 2018	0.6	Updates due to FDA review process
16 April 2018	0.7	Updates due to IND Clinical Hold response
06 August 2018	0.8	Update to DSMB due to IND Clinical Hold response
29 November 2018	0.9	Updates due to review with CRO
05 April 2019	0.10	Updates/clarifications due to review with CRO
18 June 2019	0.11	Changes made to travel compensation, Admission Day 2 made optional, clarification of inclusion criteria regarding BMI and weight, listed additional reported clinical labs, allows SURC clinic for follow-up visits where appropriate.
26 May 2020	0.12	Changes made to allow for remote study visits during the time of the COVID-19 pandemic.

18 SUMMARY OF CHANGES FROM PREVIOUS VERSION

18.1 Version 0.6

Affected Section(s)	Summary of Revisions Made	Rationale
1.0	Addition of Implantation procedure Surgeon	Identification of implantation procedure Surgeon
2.2	Update to study rationale	Clarification of health participants and reasoning
2.3	Addition of point 6 and 7	Updated risk of Naltrexone hepatotoxicity Addition of risk of Naloxone
3.1	Addition of Time for C_0 for Naltrexone Increase of monthly bloods to day 540	Extension of study so as to define time to undetectable naltrexone levels.
4.1	Update to study description	Extension of study so as to define time to undetectable naltrexone levels.
4.21	Update to primary endpoint	Extension of study so as to define time to undetectable naltrexone levels.

Affected Section(s)	Summary of Revisions Made	Rationale
4.22	Update to secondary endpoint	Extension of study so as to define time to undetectable naltrexone levels.
4.23	Update to primary efficacy endpoint	Extension of study so as to define time to undetectable naltrexone levels.
4.24	Update to secondary efficacy endpoint	Extension of study so as to define time to undetectable naltrexone levels.
5.1	Addition of healthy and assessment of general and mental health status	Clarification of healthy participants and mental health evaluation.
5.2	Update to exclusion criteria	Clarification to abnormal liver function criteria Addition of exclusion of participants at risk of suicide and the assessment tool used
5.3	Increase to number of participants	Due to extended duration of study, an increase of participants was required to ensure enough completers.
5.4.2.1	Update to section	Clarification of options for study withdrawal
7.1.1.2	Update to naloxone challenge test procedure	Update of NCT procedure to cover effects of the test and treatment of server symptoms
7.1.1.3	Update to implantation procedure	Addition of procedure from training manual
7.1.1.4	Addition of wound site/implant site assessment	Addition of protocol for assessing wound/implant site. Addition of Implant site evaluation form as appendix
7.2.1	Clarification of blood test and amount	Clarification of blood test and amount
7.2.3	Addition of total amount of blood to be collected	Addition of total amount of blood to be collected
7.3.1	Clarification of screening visit 1	Clarification of screening visit 1
7.3.2	Addition of screening visit 2	Addition screening visit added to allow more time for the participant to understand the trial
7.3.3	Update to recruitment visit	Update to recruitment visit
7.3.4	Update to baseline visits	Update due to admission of subjects on day -1 and timepoint for NCT. Clarification to text for admission day 1 and 2.

Affected Section(s)	Summary of Revisions Made	Rationale
7.3.5	Update to follow-up visit	Clarification to follow-up visit
7.3.9	Addition of PK follow-up visit	Addition of extra PK visits if required post day 540 if participants haven't recorded 2 consecutive undetectable naltrexone blood values.
7.1	Update to assessment time point table	Updated due to increased study duration and additional visits.
7.6.1	Update to prophylactic medications	Clarification of wording
7.6.2	Update to treatment of inflammatory responses	Updated protocol for dealing with inflammatory responses to the OLANI.
7.9	Update to reimbursement costs	Update due to increased number of follow-up and screening visits.
8.1.1	Update to AE definition	Clarification of wording
8.1.2	Update to definition of SAE	Removal of wording relating to non-applicable non serious adverse events.
8.2.3	Update to expected AEs	Clarification of some descriptions. Clarification of rarely seen AE's
Table 8.1	Removal of table	Table now covered in section 7.1.1.4
8.4	Update to reporting procedures	Clarification of reported, (reference to NIDA was removed until funding is clarified).
8.6.2	Update to DSM	Clarification of DSM reporting
8.6.3	Addition of DSMB plan	Addition of DSMB plan as required.
Section 10	Update to statistical consideration	Updates due to increase in study duration and participants, and change in emphasis to primary endpoints.
Section 18	Updated reference lists	Additional reference included
Throughout document	Update of subject, patient, to participant	Update of wording to ensure uniform reference to study participants where applicable.
PIC & PIS	Update of purpose and overview	Update due to extension of the study
PIC & PIS	Update of procedures	Update due to increased number of follow-up and screening visits.
PIC & PIS	Update of risk and inconveniences	Updated risk of Naltrexone hepatotoxicity Addition of risk of Naloxone

Affected Section(s)	Summary of Revisions Made	Rationale
PIC & PIS	Update to withdrawal from study	Clarification of options for study withdrawal
PIC & PIS	Update to reimbursement schedule	Update due to increased number of follow-up and screening visits.
PIC & PIS	Update to questions	Addition of 24h medical phone number

18.2 Version 0.7

Affected Section(s)	Summary of Revisions Made	Rationale
7.1.1.3	Update to the use of IV antibiotic treatment	Correction of deficiency identified in IND clinical hold response
7.1.1.4	Update to wound site/implant site assessment procedure.	Correction of deficiency identified in IND clinical hold response
7.6.1	Update to the use of IV antibiotic treatment	Correction of deficiency identified in IND clinical hold response
7.6.2	Update to management of wound site/implanted site	Clarification of treatment for infection and/or inflammation at the wound/implant site
8.6.2	Update of DSM allow ad-hoc meetings and increase frequency of meetings	Correction of deficiency identified in IND clinical hold response
8.6.3	Update to DSMB plan to include study surgeon and increase frequency of meetings	Correction of deficiency identified in IND clinical hold response

18.3 Version 0.8

Affected Section(s)	Summary of Revisions Made	Rationale
8.6.1	Update of responsibilities	Clarification of PI's responsibility
8.6.3	Update to DSMB personnel.	Replacement of study surgeon on DSMB due to deficiency identified in IND clinical hold response

18.4 Version 0.9

Affected Section(s)	Summary of Revisions Made	Rationale
VI	Update schematic of study	Update due to clarification of study visits
1.3	Update study satellite location information	Clarification of one study site, with two satellite locations
5.1	Update study inclusion/exclusion criteria	Clarification and added details of descriptions
5.4.2.1	Update description of if participant becomes pregnant	Provide additional details on discontinuation of study participation and safety monitoring
7.1.1.1	Update description	Clarification of section
7.1.1.2	Update naloxone challenge test	Provide additional details on determining whether a participant has passed the NCT
7.2.1	Update clinical laboratory evaluation section	Clarification of specific tests collected
7.3.1	Update screening visit procedures	Provide additional details on screening procedures
7.3.2	Update screening visit procedures	Provide additional details on screening procedures
7.3.5	Update follow-up visit procedures	Provide additional details on follow-up procedures and timings
7.3.6	Update final study visit schedule	Clarification of when final study visit occurs
7.3.9	Update PK follow-up visit schedule	Clarification of when PK follow-up visit occurs
7.3.11	Update terminology of table of assessments	Clarification of terminology
7.5	Reconciled prohibited medications timeframe	Clarification of timeframe excluding prohibited medication
8.6.2	Updated responsibilities of study PI	More details on study PI responsibilities as part of DSMB meetings
8.6.3	Update membership of DSMB	Dr. Kleber was removed from DSMB. Dr. Stewart and Dr. Foltin added
10.1	Update Statistical Analysis Plan	Added SAP
Appendix 1	Removal of appendix references	PIC & PIS no longer needing to be referenced

18.5 Version 0.10

Affected Section	Summary of Revisions Made	Rationale
VI	Updated to Study Schematic	Replaced GHQ and MHA with PHQ and BDI-II, respectively.
5.4.2	Added 'Screen Failure' to the list of reasons for discontinuation from the study.	Clarification made that Screen Failure will be captured as a reason for discontinuation from the study.
7.2.1	Update clinical laboratory evaluation section	Clarification of materials (i.e. types of tubes) used during sample collection. In addition, added fentanyl to the list of drugs for screening.
7.2.2	Update to Naltrexone Blood Level Assay (sampling)	Clarification to sample collection step and to total amounts of blood drawn. Removed details regarding handling and storage (moved to 7.2.4.1)
7.2.3	Update to Total Amount of Blood Collected	Updated the PK sampling volume from 9 mL to 10 mL for un-scheduled visits.
7.2.4.1	Update to Naltrexone Blood Level Assay (handling and storage)	Provide additional details regarding handling and sampling that were removed from 7.2.2.
7.2.5	Update to Specimen Shipment	Clarified that samples shall be stored at no warmer than -70ºC to set an upper limit.
7.3.1	Update screening visit procedures	Specified that the Patient Health Questionnaire (PHQ) and Beck Depression Inventory (BDI-II) will be used as the tools for the General Health Questionnaire (GHQ) and Mental Health Assessment (MHA), respectively. In addition, a breathalyzer assessment will be performed at SV1.
7.3.3	Updates to recruitment visit	Added breathalyzer assessment
7.3.4	Updates and name change to 'Baseline' section.	Changed the heading from Baseline to Day – 1 to Day 2 (Admission Days). Clarified what procedures happen during the Admission days (Day -1 to Day 2). Replaced GHQ and MHA with PHQ and BDI-II, respectively.
7.3.5	Update to follow-up visits (day 4 to 540)	Replaced GHQ and MHA with PHQ and BDI-II, respectively.

Affected Section	Summary of Revisions Made	Rationale
Table 7-1	Updates to schedule of assessments table	Updates made to correct errors and match the body of the protocol. In addition, specified that the Recent Drug Use-Baseline (RDU) and Quantitative Substance Use Inventory will be used as tools for assessing self-reported substance use.
13.4.1.1	Update to research use of stored human samples	Clarification regarding location and handling of samples.

18.6 Version 0.11

Affected Section(s)	Summary of Revisions Made	Rationale
V, 1,	Clarification that the Final Visit/Early Termination Visit occur at the SURC clinic.	Administrative/clarification.
V, 1, 7.1.1.4, 7.3.5, Table 7-1	Added language to indicated that that some follow up visits beyond 48-hours may occur at the SURC clinic.	In certain cases, it may be appropriate for follow-up visits beyond the 48-hour assessments to occur at the SURC clinic rather than the Clinilabs clinic (e.g. if the participant needs to be seen by the PI or study surgeon, or to lessen the burden of travel for the participant).
5.1	Inclusion criteria was modified so that participants need to meet the weight or BMI criteria rather than both.	Clarification that one or the other criteria need be met. Requiring both is not necessary from a clinical perspective and would exclude certain participants unnecessarily.
7.1.1.4	Changed 'Study Site 1' to SURC Clinic and 'Study Site 2' to Clinilabs clinic.	Harmonization of language in how site locations are referenced.
7.2.1	Updates made to clinical laboratory evaluations.	Upon review of the test results received from LabCorp, it was discovered that extra tests were performed on samples compared to those outlined in the study protocol. Having the extra information is not detrimental to the safety of the subjects. The tests are being added to the protocol as a clarification because this test panel will be used for all subjects.

Affected Section(s)	Summary of Revisions Made	Rationale
7.3.4	Changes made to indicated that participants have the option of being discharged from the SURC clinic after the 24-hour assessments and can participate in the 48-hour assessments as an outpatient.	This change is made to lessen the burden of the study participants given the restrictions of the psychiatric inpatient unit.
7.9	Updates made to participant reimbursement to allow for more travel compensation.	It was discovered that in most cases, the original allowance of $10 per visit for travel was not enough to cover transportation expenses.

18.7 Version 0.12

Affected Section(s)	Summary of Revisions Made	Rationale
7.3.5	Text added to indicated that some of the follow-up visits may occur via telephone or video during the COVID-19 pandemic.	Modification to study design due to the COVID-19 pandemic.
7.3.11	Footnotes to Table 7-1 were updated to clarify which assessments would occur remotely and which assessments/procedures may be missed due to the COVID-19 pandemic.	Modification to study design due to the COVID-19 pandemic.

18.8 Version 0.13

Affected Section(s)	Summary of Revisions Made	Rationale
Throughout document	Undetectable naltrexone blood levels defined as a measurement of <0.1 ng/mL.	This change allows monitoring to end within a reasonable and meaningful timeframe. With a limit of quantification of 0.02 ng/mL for naltrexone, blood levels could hover just above or below this value for an extended period with no therapeutic potential.

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