A PHARMACOKINETIC STUDY OF VIVITROL IN HEALTHY PARTICIPANTS

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term or Abbreviation	Description
6βN	6-β-naltrexol
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under the Curve
CRF	Case Report Form
CRO	Contract Research Organization
CSSRS	Columbia Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EUC	Electrolytes, Urea, Creatinine
FBE	Full Blood Examination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHQ	General Health Questionnaire
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICH	International Council for Harmonization
IP	Investigational Product
IRB	Institutional Review Board
LFT	Liver Function Tests
MHA	Mental Health Assessment
NCT	Naloxone Challenge Test
NTX	Naltrexone
NYSPI	New York State Psychiatric Institute
OLANI	O'Neil Long Acting Naltrexone Implant
PI	Principal Investigator
PIC	Participant Information Consent
PK	Pharmacokinetic
QC	Quality Control

Term or Abbreviation	Description
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UDS	Urine Drug Screen

III. SPONSOR SIGNATORY:

Chin-Tark Chan
Operations Manager
Go Medical Industries Pty Ltd.

Date: 25MAR2021

IV. STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6 GCP. 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:

March 25, 2021

Date:

V. PROTOCOL SUMMARY

Title:	**A PHARMACOKINETIC STUDY OF VIVITROL IN HEALTHY PARTICIPANTS**
Overview:	This is a Phase I, single-center, single arm, open-label study, to establish the pharmacokinetic (PK) parameters of Vivitrol 380 mg IM injection (IP), a US Food and Drug Administration (FDA) approved medication. Participants will be healthy volunteers with no significant medical or mental health disorders, who have completed participation in clinical trial GM 0017 (i.e. have received the OLANI treatment and have subsequently provided two consecutive plasma levels of naltrexone (NTX) <0.1ng/mL). This study will examine the PK profile of Vivitrol IM 380 mg over 6 doses for a treatment period of 196 days. Intense sampling will occur after the 1st and 6th dose of Vivitrol. Participants will be 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 IP. No randomization will occur. Note: In the future, an expansion of this protocol is planned in order to include additional participants that initially receive 2 doses of Vivitrol followed by the OLANI treatment (i.e. the 'cross-over' group). This expansion may occur under this same protocol ID or a new protocol ID.
Objectives:	**Primary:** • To determine the PK parameters of C_{max}, T_{max}, C_{trough} (Day 28), and AUC for the 1st and 6th dose of Vivitrol IM 380mg. **Secondary:** • To determine steady state characteristics and demonstrate no accumulation between repeat doses. • To establish the safety and tolerability of the NTX injection over 6 months.
Endpoint:	***Primary:*** • PK parameters, including C_{max}, C_{trough} (Day 28), and AUC ***Secondary:*** • To demonstrate no accumulation following repeat doses of Vivitrol IM 380 mg. Safety endpoints will be captured through 6 months and will include the incidence of adverse events (AEs) including: • deaths • serious adverse events (SAEs) • AEs leading to discontinuation • common AEs

	• AEs of special interest (injection site reactions and hepatic effects) • laboratory abnormalities (absolute values and changes over time in laboratory parameters) • the proportion of participants who discontinue treatment due to AEs)
Population:	Up to 6 healthy participants to be recruited (with 4 required to complete the study), aged at least 18 (≥18) and no older than 57 (<58), without a DSM 5 - Substance Related Disorders classification, residing within the New York metropolitan area. Participants are to be recruited with the perquisite of having successfully finished study GM 0017.
Phase:	I
Number of Sites:	Two Site 1: New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA (administration center for PI) Site 2: Clinilabs, 423 West 55th St, New York, 10019 (Vivitrol reference dose administration and follow-up visits)
Investigational Product:	The investigational product (IP) (intended reference product) is a Vivitrol Intramuscular injection, 380 mg (six doses given 28 days apart)
Study Duration:	Estimated 9 months
Participant Duration:	196 days

VI. SCHEMATIC OF STUDY DESIGN

Screening and recruitment	Naloxone challenge test	IP administration Vivitrol 380 mg IM injection	PK Sampling schedule for each injection	Endpoint
As per protocol	Pass required	1st Dose – Day 0	Day 0 (predose, +1, 2, 4, 8, 12 & 24 hours), 1.5, 1.75, 2, 3, 5, 7, 10, 14, 17, 21, 24, 28	Day 28 and Day 168 trough level measurement
		2nd Dose – Day 28	Day 56	
		3rd Dose – Day 56	Day 84	
		4th Dose – Day 84	Day 112	
		5th Dose – Day 112	Day 140	
		6th Dose – Day 140	Day 140 (1, 2, 4, 8 & 12 hours), 141, 141.5, 141.75, 142, 143, 145, 147, 150, 154, 157, 161, 164, 168, 182, and 196	

1 KEY ROLES

1.1 SPONSOR

Go Medical Industries Pty Ltd,
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1.2 PRINCIPAL INVESTIGATOR

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1.3 SITE 1

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(Administrative center)

1.4 SITE 2

Clinilabs, 423 West 55th St, New York, 10019
(IP administration and follow-up)

1.5 CLINICAL LABORATORY

(NALTREXONE AND 6-β-NALTREXOL BLOOD ANALYSIS ONLY)
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Tel: 609-606-6620; Fax: 609-799-7497

1.6 CENTRAL CLINICAL LABORATORY

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

1.7 RESPONSIBLE CLINICIAN

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1.8 MEDICAL MONITOR

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1.12 CLINICAL TRIAL CO-ORDINATOR

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1.14 CLINICAL RESEARCH ASSOCIATE

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC

2.1 BACKGROUND INFORMATION

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 (Vivitrol).

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. NTX is extensively metabolized in humans[1]. Production of the primary metabolite, 6β-naltrexol (6βN), 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 NTX[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 PK 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 effective 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 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.

2.1.4 Investigational Product: Vivitrol IM 380 mg

In 2006, a 30 day NTX intramuscular injection known as Vivitrol (Alkermes) was approved by the FDA for the treatment of alcohol dependence, and it was also approved 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 mean trough naltrexone blood level above 1.33 ng/ml for approximately four weeks[22].

Vivitrol PK will be captured in the present study to be used as a reference product in [redacted] drug application for the OLANI product which is being developed under [redacted]

2.2 STUDY RATIONALE

This is a Phase I, single-center, single arm, open-label study to determine PK parameters for Vivitrol 380 mg IM which is an FDA approved formulation. The PK characteristics of Vivitrol can then be used as the approved comparator product in a [redacted] application for OLANI.

Participants will be healthy volunteers with no opioid or other substance use disorders and no other significant medical or mental health disorders. It should be noted that participants from Clinical Trial GM 0017 have already received the OLANI treatment and have subsequently provided two consecutive plasma levels of NTX <0.1 ng/mL. Only these participants shall be offered recruitment into the study to allow for the inter-individual comparison of Vivitrol and OLANI PK parameters.

Note: In the future, an expansion of this protocol is planned in order to include additional participants that initially receive 2 doses of Vivitrol followed by the OLANI treatment (i.e. the 'cross-over' group). This expansion may occur under this same protocol ID or a new protocol ID.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 Known Potential Risks

The following sections (1-11) are taken from *Section 5 of* the Vivitrol *US Prescribing Information*[23] which should be consulted for detailed information**.**

1. Vulnerability to Opioid Overdose

After opioid detoxification, patients are likely to have reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after

administration. However, as the blockade wanes and eventually dissipates completely, patients who have been treated with VIVITROL may respond to lower doses of opioids than previously used, just as they would have 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. Cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment.

Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after VIVITROL treatment is discontinued, especially at the end of a dosing interval (i.e., near the end of the month that VIVITROL was administered), or after a dose of VIVITROL is missed. It is important that patients inform family members and the people closest to the patient of this increased sensitivity to opioids and the risk of overdose.

There is also the possibility that a patient who is treated with VIVITROL could overcome the opioid blockade effect of VIVITROL. Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. The plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Any attempt by a patient to overcome the antagonism by taking opioids is especially dangerous and may lead to life-threatening opioid intoxication or fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade.

2. Injection Site Reactions

VIVITROL must be prepared and administered by a healthcare provider. VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe. In the clinical trials, one patient developed an area of induration that continued to enlarge after 4 weeks, with subsequent development of necrotic tissue that required surgical excision. In the postmarketing period, additional cases of injection site reaction with features including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis, have been reported. Some cases required surgical intervention, including debridement of necrotic tissue. Some cases resulted in significant scarring. The reported cases occurred primarily in female patients.

VIVITROL is administered as an intramuscular gluteal injection, and inadvertent subcutaneous injection of VIVITROL may increase the likelihood of severe injection site reactions. The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1 1/2 or 2 inches) may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that the proper needle is selected and that the needle length is adequate for intramuscular administration. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1 1/2-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. Healthcare providers should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles.

Patients should be informed that any concerning injection site reactions should be brought to the attention of the healthcare provider. Patients exhibiting signs of abscess, cellulitis, necrosis, or extensive swelling should be evaluated by a physician to determine if referral to a surgeon is warranted.

3. Precipitation of Opioid Withdrawal

The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Review of postmarketing cases of precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit.

To prevent occurrence of precipitated withdrawal in patients dependent on opioids, or exacerbation of a pre-existing subclinical withdrawal syndrome, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting VIVITROL treatment. An opioid-free interval of a minimum of 7–10 days is recommended for patients previously dependent on short-acting opioids. Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks.

If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed.

In every case, healthcare providers should always be prepared to manage withdrawal symptomatically with non-opioid medications because there is no completely reliable method for determining whether a patient has had an adequate opioid-free period. A naloxone challenge test may be helpful; however, a few case reports have indicated that patients may experience precipitated withdrawal despite having a negative urine toxicology screen or tolerating a naloxone challenge test (usually in the setting of transitioning from buprenorphine treatment). Patients should be made aware of the risks associated with precipitated withdrawal and encouraged to give an accurate account of last opioid use. Patients treated for alcohol dependence with VIVITROL should also be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of treatment with VIVITROL. Precipitated opioid withdrawal has been observed in alcohol-dependent patients in circumstances where the prescriber had been unaware of the additional use of opioids or co-dependence on opioids.

4. Hepatoxicity

Cases of hepatitis and clinically significant liver dysfunction were observed in association with VIVITROL exposure during the clinical development program and in the postmarketing period. Transient, asymptomatic hepatic transaminase elevations were also observed in the clinical trials and postmarketing period. Although patients with clinically significant liver disease were not systematically studied, clinical trials did include patients with asymptomatic viral hepatitis infections. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs. Although clinically significant liver dysfunction is not

typically recognized as a manifestation of opioid withdrawal, opioid withdrawal that is precipitated abruptly may lead to systemic sequelae including acute liver injury.

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis.

5. Depression and Suicidality

Alcohol- and opioid-dependent patients, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking. Families and caregivers of patients being treated with VIVITROL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's healthcare provider.

Alcohol Dependence

In controlled clinical trials of VIVITROL administered to adults with alcohol dependence, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in patients treated with VIVITROL than in patients treated with placebo (1% vs 0%). In some cases, the suicidal thoughts or behavior occurred after study discontinuation, but were in the context of an episode of depression that began while the patient was on study drug. Two completed suicides occurred, both involving patients treated with VIVITROL.

Depression-related events associated with premature discontinuation of study drug were also more common in patients treated with VIVITROL (~1%) than in placebo-treated patients (0%).

In the 24-week, placebo-controlled pivotal trial in 624 alcohol-dependent patients, adverse events involving depressed mood were reported by 10% of patients treated with VIVITROL 380 mg, as compared to 5% of patients treated with placebo injections.

Opioid Dependence

In an open-label, long-term safety study conducted in the US, adverse events of a suicidal nature (depressed mood, suicidal ideation, suicide attempt) were reported by 5% of opioid-dependent patients treated with VIVITROL 380 mg (n=101) and 10% of opioid-dependent patients treated with oral naltrexone (n=20). In the 24-week, placebo-controlled pivotal trial that was conducted in Russia in 250 opioid-dependent patients, adverse events involving depressed mood or suicidal thinking were not reported by any patient in either treatment group (VIVITROL 380 mg or placebo).

6. When Reversal of VIVITROL Blockade Is Required for Pain Management

In an emergency situation in patients receiving VIVITROL, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required as part of anesthesia or analgesia, patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

Irrespective of the drug chosen to reverse VIVITROL blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

7. Eosinophilic Pneumonia

In clinical trials with VIVITROL, there was one diagnosed case and one suspected case of eosinophilic pneumonia. Both cases required hospitalization, and resolved after treatment with antibiotics and corticosteroids. Similar cases have been reported in postmarketing use. Should a person receiving VIVITROL develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered. Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia. Clinicians should consider the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics.

8. Hypersensitivity Reactions Including Anaphylaxis

Cases of urticaria, angioedema, and anaphylaxis have been observed with use of VIVITROL in the clinical trial setting and in postmarketing use. Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis. In the event of a hypersensitivity reaction, patients should be advised to seek immediate medical attention in a healthcare setting prepared to treat anaphylaxis. The patient should not receive any further treatment with VIVITROL.

9. Intramuscular Injections

As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (e.g., hemophilia and severe hepatic failure).

10. Alcohol Withdrawal

Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

11. Interference with Laboratory Tests

VIVITROL may be cross-reactive with certain immunoassay methods for the detection of drugs of abuse (specifically opioids) in urine. For further information, reference to the specific immunoassay instructions is recommended.

12. Known side-effects from NTX 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.

13. Naloxone injection may cause withdrawal symptoms in individuals who are opioid dependent including 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 as robust PK data will allow for the ongoing development of the OLANI product.

3 OBJECTIVES AND PURPOSE

3.1 PRIMARY OBJECTIVES

To determine the PK parameters of C_{max}, T_{max} and AUC for the 1st and 6th dose of Vivitrol IM 380 mg, and C_{trough} for the 1st through 6th dose. C_{trough} is defined as the naltrexone level obtained 28 days after each dose. PK parameters will be collected over a treatment period of 196 days.

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

- Day 0 (predose, +1, 2, 4, 8, 12 & 24 hours), 1.5, 1.75, 2, 3, 5, 7, 10, 14, 17, 21, 24, 28,
- Day 56, 84, 112 days,
- Day 140 (predose +1, 2, 4, 8 & 12 hours), 141, 141.5, 141.75, 142, 143, 145, 147, 150, 154, 157, 161, 164, 168, 182, and 196 days

3.2 SECONDARY OBJECTIVES

- To confirm no accumulation between repeat doses
- To determine the safety and tolerability of Vivitrol over 196 days.

Safety endpoints will be captured throughout and will include the incidence of AEs including:

- deaths
- SAEs
- AEs leading to discontinuation
- common AEs
- AEs of special interest (injection site reactions and hepatic effects)
- laboratory abnormalities (absolute values and changes over time in laboratory parameters)
- the proportion of participants who discontinue treatment due to AEs)

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

Participants who have completed the study end points of GM 0017 (i.e. two consecutive monthly plasma results <0.1 ng/mL for NTX) will be offered enrolment into the study.

Up to 15 participants will be recruited onto this arm with 12 expected to complete to full dosing and sampling schedule.

Participants will receive a 380 mg Vivitrol IM injection and blood samples will be taken according to the sampling schedule of Table 7-1. Subsequently, participants will be re-administered Vivitrol injections every 28 days for a total of 6 Vivitrol injections. Blood sampling will be performed as per Table 7-1. The administration of 6 repeated Vivitrol injections is to confirm the published findings that no accumulation of Vivitrol is evident after repeated injections and to allow a direct time frame comparison to future bioequivalence study with OLANI.

This PK information, including day 28 naltrexone trough level, is needed so that Vivitrol can be used as the reference product for previous and future studies of OLANI.

4.2 STUDY ENDPOINTS

4.2.1 Primary Endpoint

- The collection of at least 75% of the PK blood samples including respective day 28 blood collections for 1st and 6th injection phase.

4.2.2 Secondary Endpoints

Safety endpoints will be captured through 6 months and will include the incidence of AEs including:

- deaths
- SAEs
- AEs leading to discontinuation
- common AEs
- AEs of special interest (injection site reactions and hepatic effects)
- laboratory abnormalities (absolute values and changes over time in laboratory parameters
- the proportion of participants who discontinue treatment due to AEs

4.2.3 Primary Efficacy Endpoint:

- Establishment of reference product Vivitrol 28-day naltrexone trough blood level.
- Mean Cmax, Tmax, AUC, Ctrough for NTX blood level
- Mean Cmax, Tmax, AUC, Ctrough for 6βN blood level

4.2.4 Secondary Efficacy Endpoints:

- Frequency of AEs and SAEs

5 STUDY ENROLLMENT 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 IP.

To qualify for the study participation, participants have to:

- Have completed GM 0017 (i.e. been administered OLANI (3.6 gram) and provided two consecutive monthly blood samples of NTX below 0.1 ng/mL)
- Men or women aged at least 18 (≥18) and no older than 57 (<58), without DSM 5 - Substance Related Disorders classification; in sustained remission is not exclusionary
- Able and willing to comply with the requirements of the protocol
- Able and willing to provide written informed consent
- Willing to undergo an injection of NTX to allow for investigational drug administration in the intramuscular tissue
- 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

Participants will not be eligible for the study if they meet any of the following criteria:

- Is currently on active NTX medication.
- Positive UDS at screening for illicit substances.
- Has a condition which requires treatment with opioid based medication.
- Has a known hypersensitivity to NTX.
- Is prone to skin rashes, irritation or has a skin condition such as recurrent eczema that is likely to impact the injection site area, or as determined by the evaluating physician.
- Demonstrates any abnormal skin tissue in the proposed injection area.
- Is pregnant or planning to be. Women need to have negative pregnancy test at screening. Women need to agree to practice an effective method of contraception throughout participation.
- Participant is breastfeeding or planning to be.
- Has a current significant neurological (including cognitive and psychiatric disorders),
- Any clinically important abnormal finding as determined by medical history, physical examination, ECG or clinical laboratory tests.
- 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.

- ALT or AST >3 times the upper end of the laboratory normal range.
- Any methadone use 14 days prior to screening, and up to Study Day 0.
- 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.
- 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)
- Is participating or intending to participate in any other clinical trial during the duration of this study.
- Is allergic to any of the ingredients in Vivitrol or the diluent used to mix Vivitrol (i.e. carboxymethylcellulose sodium, polysorbate 20, sodium chloride, sodium hydroxide and hydrochloric acid as pH adjusters, in water for injection).

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

5.3.1 Target Sample Size

Recruitment into the study will be solely offered to the 19 participants who have completed the previous study GM 0017. Up to 15 participants from GM 0017 will be targeted for recruitment to this study. We expect that 12 of the 15 participants will complete the study (80%), which is providing at least 75% valid PK blood samples including Day 28 and Day 168 Vivitrol trough levels.

5.3.2 Recruitment

All participants will be seen by a study clinician (MD or PA) for a screening evaluation and mental status examination as part of routine admission procedures at Clinilabs. Final informed consent for the study will be obtained after full medical workup is complete. The research staff knows the protocol well, and is able to explain study to the participant. Procedures for training study clinicians in the 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.

Study participation will only be offered to those that have successfully completed GM 0017 and therefore no advertising for recruitment outside of GM 0017 participants is required.

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 a 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 abnormalities 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.

5.4.2 Handling of Participant Withdrawals or Termination

Participants, who do not receive the IP (i.e. Vivitrol), for any reason, are not considered study 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

5.4.2.1 Participant Monitoring and Removal from Study

The psychiatrist and/or therapist will assess 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 drug binges (including non-opiate drugs).
2. Elevation of liver enzymes >3 times normal. The PI or a study physician is available 24 hours/day by phone in case of emergency.

For those who withdraw from the study may request to withdraw from data collection and have no further contact with study site. Participants shall be informed that for a period of time 30 days after their last Vivitrol injection there may a risk that opioid based medication may have a reduced affect. There is no option to remove Vivitrol from a participant.

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, Data Safety Monitoring Panel (DSMP), 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

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

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 Acquisition

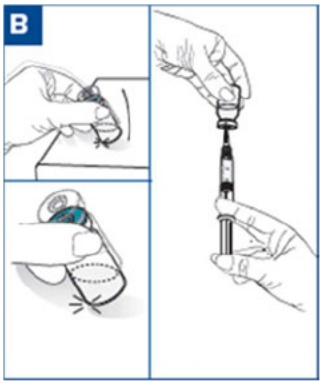
Vivitrol as manufactured by Alkermes, will be sourced from commercially available suppliers

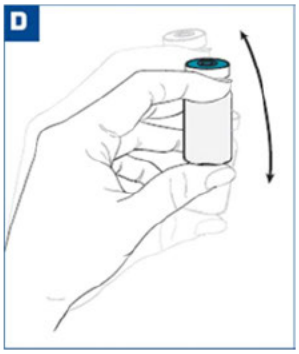
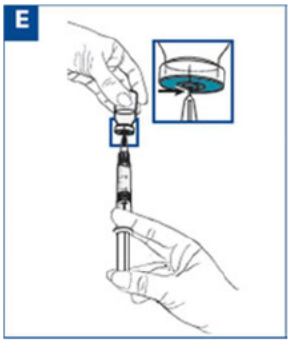
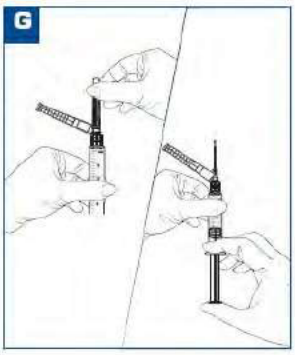
6.1.2 Formulation, Appearance, Packaging and Labelling

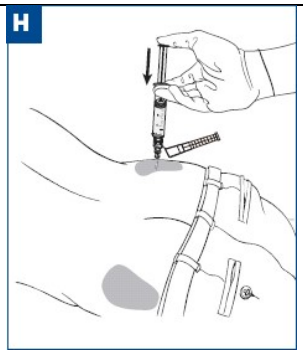
6.1.2.1 Manufacturing and Sterility

Vivitrol is an FDA approved product manufactured by Alkermes. Vivitrol is a sterile IM injection and is to be used as a reference drug product in the development of the OLANI and shall be sourced from commercially available supplies.

6.1.2.2 Packaging

	1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes). 2. To ease mixing, firmly tap the VIVITROL Microspheres vial on a hard surface, ensuring the powder moves freely. (see Figure B) 3. Remove flip-off caps from both vials. DO NOT USE IF FLIP-OFF CAPS ARE BROKEN OR MISSING. 4. Wipe the vial tops with an alcohol swab. 5. Place the 1 inch preparation needle on the syringe and withdraw 3.4 mL of the diluent from the diluent vial. Some diluent will remain in the diluent vial.
	1. Inject the 3.4 mL of diluent into the VIVITROL Microsphere vial.

	2. Mix the powder and diluent by vigorously shaking the vial for approximately 1 minute. 3. Ensure that the dose is thoroughly suspended prior to proceeding to Step E.
	1. Immediately after suspension, withdraw 4.2 mL of the suspension into the syringe using the same preparation needle. (see Figure E) 2. Select the appropriate needle for an intramuscular injection based on patient's body habitus: a. 1.5 inch TERUMO Needle b. 2 inch NEEDLE-PRO Needle
	1. Remove the preparation needle and replace with appropriately selected administration needle for immediate use. 2. Peel the blister pouch of the selected administration needle open halfway. Grasp sheath using the plastic pouch. Attach the luer connection to the syringe with an easy clockwise twisting motion. 3. Seat the needle firmly on the needle protection device with a push and clockwise twist.
	1. Pull the sheath away from the needle – do not twist the sheath because it could result in loosening the needle. 2. Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until 4 mL of the suspension remains in the syringe. THE SUSPENSION IS NOW READY FOR IMMEDIATE ADMINISTRATION.

	1. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per monthly injection. 2. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection. 3. Inject the suspension in a smooth and continuous motion.

6.1.2.3 Disposal

Dispose of as per manufacturer's instructions.

6.1.3 Product Storage and Stability

The entire dose kit should be stored in the refrigerator (2-8 °C, 36-46 °F). Unrefrigerated, VIVITROL Microspheres can be stored at temperatures not exceeding 25 °C (77 °F), for no more than 7 days prior to administration. Unrefrigerated Vivitrol should not be exposed to temperatures above 25 °C (77 °F). VIVITROL should not be frozen.

6.1.4 Preparation

Refer to manufacturer's product information sheet.

6.1.5 Dosing and Administration

Participants shall be dosed as per the schedule outlined in Table 7-1.

6.1.6 Route of Administration

Intramuscular injection in the buttock region (gluteal muscle) as per manufacturer's product information sheet. [23]

6.1.7 Dose Adjustments/Modifications/Delays

Not applicable

6.1.8 Duration of Therapy

Time in therapy: 196 days

Total anticipated study length (including recruitment): 9 months

6.1.9 Tracking of Dose

All participants will be administered a single Vivitrol injection into the gluteal muscle as per the schedule in Table 7-1, alternating between left and right gluteal muscle as tolerated, with the exact site being recorded.

All follow up visits will check for AE's related to the IP and where appropriate any injection site reactions.

6.1.10 Device Specific Considerations

Not applicable.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Vivitrol for the study shall be sourced from a commercial supplier by the PI. The PI (or delegated study personnel) will sign that they have received all IP. IP will be kept in a securely locked refrigerated cabinet under appropriate temperature conditions and a drug inventory and temperature log maintained. All unused supplies must be accounted for and destroyed with an appropriate certificate of destruction 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 Screening

The Screening Visit (conducted at Clinilabs) will include assessments necessary to determine study eligibility. The nature of the study and its risks and benefits will be explained to the participant by the study clinician 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 IP administration are discussed in great detail. The study clinician (MD or PA) will perform a medical and psychiatric evaluation including a medical history and a physical examination. Medical staff or certified research assistants obtain electrocardiogram (ECG) and blood for complete blood count with differential, chemistry profile, liver function tests and pregnancy tests (if applicable). Urine is obtained for urinalysis and toxicology.

7.1.1.2 Recruitment Visit

Study-trained medical professionals such as a physician or a physician assistant that has been medically trained by the study PI to consent participants to the study and provide them with all necessary medical information will discuss questions related to the study procedure and the consent form. During the Recruitment Visit (conducted at Clinilabs) a study-trained medical professional confirms that a participant meets all inclusion/exclusion criteria, is medically healthy to participate in the study. A study-trained medical professional 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 a study-trained medical professional reviewed results of the evaluation and obtained informed consent. Following study enrollment, a study-trained medical professional assumes medical responsibility and arranging hospitalization for IP administration at Clinilabs followed by in-patient care at Clinilabs.

7.1.1.3 Naloxone challenge test (NCT)

All participants will undergo an NCT at Clinilabs prior to IP administration. Participants will receive 0.8 mg naloxone, IM, followed by q10 minutes observation by study clinician or nurse over 30 minutes for signs and symptoms of opiate withdrawal.

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 IP administration with the injection procedure (see Section 7.1.1.4).

7.1.1.4 Injection procedure (initial)

Following a successful NCT, the injection of IP (Vivitrol), is to be performed as per the manufacturer's instructions[23]. The injection will be performed at the Clinilabs site. Participants will then remain at the Clinilabs research facility for 48 hours so that intensive

portion of the blood collection can occur.

7.1.1.5 Injection procedure (repeat dose)

There are 4 instances whereby participants will be re-administered Vivitrol 28 days apart with no intensive blood monitoring scheduled following re-administration of Vivitrol and no overnight stay. These are for Vivitrol injections 2, 3, 4 and 5 as outlined in Table 7-1. In these instances, participants will be seen on an out-patient basis at Clinilabs for their re-administration of Vivitrol. Just prior to re-administration of Vivitrol, a NTX blood sample will be collected to capture the Vivitrol/naltrexone trough level. The actual time of each PK sample collection shall be recorded relative to the re-administration of Vivitrol.

There are 2 instances whereby participants are administered Vivitrol injections and then remain at the Clinilabs research facility for intensive blood collections. These instances, Vivitrol injections 1 and 6, are detailed in depth in the admissions descriptions of 7.3.3.1, 7.3.3.2, 7.3.3.3 and 7.3.3.4.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 Clinical Laboratory Evaluations

Samples will be collected in accordance with Clinilab's procedures and sent for analysis to Lab Corp.

For the following test, 4.5 mL of blood will be collected in 1 x EDTA tube:

- *[FBC] Full Blood Count*

For the following tests, 5 mL of blood will be collected in 1 x SST tubes:

- *[EUC] Electrolytes, Urea, Creatinine*
- *[LFT] Liver function Tests (bilirubin, ALP, GGT, ALT, ALB, TP)*

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

- *Urinalysis; LEU (Leucocytes), NIT (Nitrite), PRO (Protein), pH, BLD (Blood), SG (Specific Gravity), KET (Ketones), GLU (Glucose)*
- *[UDS] Full drug screen including buprenorphine assay.*

Pregnancy test: 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 Assay

1 x 10 mL of whole blood in Na Heparin tubes (9 mL). Samples will be centrifuged for 15 min at 2,000 rpm. Plasma will then be extract and stored in suitable containers (1.5 mL Eppendorf's) for storage at -80ºC for transport to WuXi laboratories under dry ice in batches for free (unconjugated) NTX and free (unconjugated) 6βN analysis.

7.2.3 Total amount of Blood to be collected

The amount of blood drawn for the study is:

- Total LFT, EUC 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 NTX / 6βN
  - 387 mL (43 x 9 mL)
- There is also the potential for further bloods to be taken on any un-scheduled visit for PK bloods (9 mL) and follow-up visit for outstanding AEs (LFT, EUC and FBC 9.5 mL) post end of trial.

The total scheduled blood collection is approximately 581.5 mL over the period of 196 days.

7.2.4 Specimen Preparation, Handling and Storage

7.2.4.1 Naltrexone PK Blood Samples

All NTX blood samples will be collected in 1 x 10.0 mL Na Heparin tubes (9 mL) and stored in the study site refrigerator at 0-4°C until specimen preparation.

Specimen preparation will be carried out at study site within 24 hours. This will involve centrifugation of the blood sample to enable plasma separation. Plasma will be extracted and stored in suitable containers (1.5 mL Eppendorf's) and stored at -80°C. When batches of greater than 50 samples are available these can then be shipped on dry ice to WuXi Laboratories for analysis. Backup samples will remain stored at Clinilabs for the duration of the trial.

7.2.5 Specimen Shipment

Plasma will be stored for batch shipment to WuXi Laboratories, 107 Morgan Lane, Plainsboro, NJ, 08536 for analysis. Storage of samples at -80°C will be done at Clinilabs. Shipment of samples from Clinilabs to WuXi will be done under dry ice.

7.3 STUDY SCHEDULE

7.3.1 Screening Visit

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 examinations, including Patient Health Questionnaire (PHQ-9), Beck Depression Inventory (BDI)-II, and C-SSRS to determine eligibility based on inclusion/exclusion criteria.
- Concomitant medication review
- Collect blood for LFT, FBE and EUC.
- Collect blood for NTX and 6βN measurement.
- Collect blood/urine for pregnancy test in female participants.

- Self-reported substance use and UDS

7.3.2 Recruitment

At the Recruitment visit the following will take place;

- Obtain informed consent for IP administration.
- Concomitant medication review

7.3.3 IP Administration (in-patient care)

7.3.3.1 Admission Day 0

Participants will be admitted to Clinilabs where they will complete the PHQ-9, BDI-II, Substance Use assessment, concomitant medication review, AE monitoring and provide a blood/urine sample for pregnancy testing. Each participant will then undergo the NCT to confirm absence of opiate physical dependence. Participants will be scheduled to for administration of Vivitrol at Clinilabs as outlined in section 7.1.1.4. When feasible, 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 NTX and 6βN. Processing and storage of blood samples shall be done as per section 7.2.4.1.

NTX blood samples (see section 7.2.4.1) will be collected at the following time points: baseline (before Vivitrol administration), 1 hour ±15 min, 2 hours ±15 min, 4 hours ±30 min, 8 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, Vital Signs and concomitant medication review.

7.3.3.2 Admission Day 1

NTX blood samples (see section 7.2.4.1) will be collected at 24 hours ±2 hours, 36 hours ±2 hours and 42 hours ±2 hours after Vivitrol administration. The actual time of each PK sample collection shall be recorded.

Participants will also be monitored for AEs and concomitant medication review.

7.3.3.3 Admission Day 2

NTX blood samples (see section 7.2.4.1) will be collected at 48 hours ±2 hours after Vivitrol administration. The actual time of each PK sample collection shall be recorded.

Participants will also be monitored for AEs and concomitant medication review.

Participants will then be discharged and provided with a timetable for their follow-up visits, which will be carried out at Clinilabs.

7.3.3.4 Admission Day 140 to 142

NTX blood samples (see section 7.2.4.1) will be collected at 140 days ± 1 day sample prior to Vivitrol re-administration. Participants will then be administered their sixth and final Vivitrol IM injection on Day 140 and the time recorded. NTX blood samples will be collected at 140 days +1 hr ±15 min, 140 days +2 hr ±15 min, 140 days +4 hr ±30 min, 140 days +8 hr ± 60 min, 140 days +12 hr ±60 min, 141 days ± 2 hr, 141.5 days ±2 hr, 141.75 days ±2 hr, 142 days ±2 hr under in-patient care. The actual time of each PK sample collection shall be recorded. Participants will then be discharged and provided with a timetable for their follow-

up visits, which will be carried out at Clinilabs.

Participants will also be monitored for AEs, concomitant medication review, Substance Use: Self report & UDS. Where applicable, a pregnancy test will also be conducted.

7.3.3.5 Vivitrol re-administration Day 28, 56, 84 & 112 (±1 day)

There will be no intensive blood monitoring scheduled after administration of the 2nd, 3rd, 4th and 5th dose of Vivitrol as outlined in Table 7-1. In this instance, participants will be seen on an out-patient basis at Clinilabs for their re-administration of Vivitrol. Just prior to re-administration of Vivitrol, blood samples will be taken for: LFT, EUC & FBE; and NTX PK analysis to capture the Vivitrol trough level. The actual time of each PK sample collection shall be recorded relative to the re-administration of Vivitrol.

Participants will also be monitored for the following: AEs, PHQ-9, BDI-II, CSSRS, concomitant medication review, Vital signs, substance Use (Self report) and UDS. Where applicable a pregnancy test will also be conducted.

7.3.4 Follow-Up

Participants will be instructed to attend the Clinilabs facility to continue study procedures 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. At these time points, PK blood will be collected along with an injection Site assessment where applicable, PHQ-9 & BDI-II, concomitant medication review and AE monitoring.

7.3.5 Final Study Visit

All participants will be required to attend the Clinilabs study site for a final visit with a study clinician as outlined in Table 7-1.

Participants will be monitored for the following: AEs, PHQ-9, BDI-II, CSSRS, concomitant medication review, Vital signs, substance Use (Self report) and UDS.

7.3.6 Early Termination Visit

Any participants that are withdrawn will be requested to attend Clinilabs for an early termination /withdrawal visit as outlined in Table 7-1. Participants will be advised of their option 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).

7.3.7 Unscheduled/Late Visits

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. 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 have been recruited to aim for a total of 4 completers.

Participants will be asked to complete the following as a minimum; concomitant medication review, Vital signs, PK blood collection and AE monitoring.

7.3.8 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. 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).

7.3.9 Assessment Time Point Table

Table 7-1: Assessment Time Points

Visit description	Demographics, Medical/psychiatric history review	Physical & Mental Status exam, ECG	Concomitant medication review	PHQ-9, BDI & CSSRS[1]	Informed consent	LFT, EUC & FBE blood collection	Pregnancy test[2]	Adverse Event Monitoring[3]	Substance Use: Self report & UDS	Vital signs	NCT & COWS[4]	PK Blood collection[5,6]	Vivitrol administration[7]
Screening visit	X	X	X	X	X	X	X		X	X		X	
Recruitment			X		X			X		X			
Admission Day 0, 1, and 2			X	X			X	X	X	X	X	X	X
Day 3, 5, 7, 10, 14, 17, 21 & 24 (± 1 day)			X	X				X		X		X	
Day 28, 56, 84 & 112 (± 1 day)			X	X		X	X	X	X	X		X	X
Admission Day 140, 141, and 142			X	X		X	X	X	X	X		X	X
143 days ± 6hr			X					X		X		X	
Day 145, 147, 150, 154, 157, 161, 164, 168 (±1 day)			X	X			X	X	X	X		X	
Day 182 (± 2 day)			X	X				X		X		X	
Day 196 (Final Visit) (± 2 day)		X	X	X		X		X	X	X		X	
Early Termination		X	X	X		X		X	X	X		X	
Unscheduled/Late visit			X	X				X		X		X	
AE Follow-up			X	X		X		X		X			

1. CSSR-S Lifetime will be completed at screening, C-SSRS will be used to assess suicidal risk since the last visit.
2. Pregnancy testing will be conducted on all females on serum during screening and will be continued with urine testing monthly afterwards.
3. 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.
4. NCT/COWS will be done during Day 0
5. PK Collection to be performed at: 1hr ± 15min, 2hr ± 15min, 4hr ± 30min, 8hr ± 60min, 12hr ± 60min, 24hr ± 2hr (day 1), 1.5 days ± 2hr, 1.75 days ± 2hr, 2days ± 2hr, 3 days ± 6hr, 5 days ± 1 day, 7 days ± 1 day, 10 days ± 1 day, 14 days ± 1 day, 17days ± 1 day, 21 days ± 1 day, 24 days ± 1 day, 28 days ± 1 day sample before redose, 56 days ± 1 day sample before redose, 84 days ± 1 day sample before redose, 112 days ± 1 day sample before redose, 140 days ± 1 day sample before redose, 140 days + 1hr ± 15min, 140 days + 2hr ± 15min, 140 days + 4hr ± 30min, 140 days + 8hr ± 60min, 140 days + 12hr ± 60min, 141 days ± 2hr, 141.5 days ± 2hr, 141.75 days ± 2hr, 142 days ± 2hr, 143 days ± 6hr, 145 days ± 1 day, 147 days ± 1 day, 150 days ± 1 day, 154 days ± 1 day, 157 days ± 1 day, 161 days ± 1 day, 164 days ± 1 day, 168 days ± 1 day, 182 days ± 2 days, 196 days ± 2 days.
6. PK collection and/or safety bloodwork should be conducted for late visits, not unscheduled visits. PK collection and safety bloodwork may be performed during an unscheduled visit if it is within a participant's study visit window.
7. Vivitrol injection will be administered on Day 0 and on a monthly (28 days) basis afterwards days for a total of six injections. Study window for Vivitrol is ± 2 days, the earliest a participant can receive their next injection is two days before their scheduled visit; the latest they can receive it is two days after their study visit.

7.4 CONCOMITANT MEDICATIONS, TREATMENTS AND PROCEDURES

All concomitant prescription medications including non-opiate medications taken at least 90 days before study enrollment and 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
- **Extended release naltrexone (e.g., Vivitrol)** is prohibited for at least 60 days prior to Day 0 and for the duration of the study unless administered under this trial protocol.

7.6 PROPHYLACTIC MEDICATIONS, TREATMENTS AND PROCEDURES

7.6.1 Prophylactic Medications

N/A

7.7 RESCUE MEDICATIONS, TREATMENTS AND PROCEDURES

Since NTX 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 the screening visit
- $50 for the consent visit
- $200 for each inpatient day (4 days)
- $50 for each scheduled outpatient visit (23 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.

The total amount of reimbursement should a participant attend every scheduled visit is $4,580. If a participant is required to return for further PK or AE follow-up visits, or an unscheduled visit due to public health emergency then they will receive $50. In addition, participants will also receive $10 for transportation reimbursement.

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 injection 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.

8.1.1.1 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 IP, 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, DSMP 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 IP

The clinician's assessment of an AE's relationship to the IP (i.e. Vivitrol) 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 IP 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 Events from the use of Vivitrol

Common side effects of Vivitrol may include:

- *sleepiness*
- *headache*
- *dizziness*
- *vomiting*
- *decreased appetite*
- *painful joints*
- *muscle cramps*
- *cold symptoms*
- *trouble sleeping*
- *toothache*

Serious side effects may include:

- *Depressed mood*
- *Pneumonia, symptoms include;*
    - *shortness of breath or wheezing*
    - *coughing that does not go away*
- *Serious allergic reactions, symptoms include;*
    - *skin rash*
    - *swelling of your face, eyes, mouth, or tongue*
    - *trouble breathing or wheezing*
    - *chest pain*
    - *feeling dizzy or faint*

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 (as defined in 8.4) 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 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 will keep records of all AE's on an ongoing basis. Significant concerns or unexpected AE's from Dr. Adam Bisaga and Dr. Ned Nunes are to be reviewed by the DSMB via email or conference call. The Sponsor will update the protocol regularly with any new safety information relating to the drug.

8.4.2 Serious Adverse Event Reporting

All SAEs should be reported as appropriate to the Sponsor, NYSPI IRB, FDA and Data Safety Monitoring Panel (DSMP) except for those SAEs that the protocol or other document (e.g., Manufacturer's labelling) identifies as not needing expedited reporting. The expedited

reports should be followed promptly by detailed, written reports. The 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 IP, will be reported to the NYSPI IRB and DSMP. The initial SAE report will be followed by submission of a completed SAE report to both institutions. The PI and study monitor will evaluate SAEs and bring them to the attention of the DSMB at the next scheduled meeting or sooner it there are significant concerns.

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 SAE has resolved or stabilized with no further change expected, is clearly unrelated to IP, or results in death. Outcome of SAEs will be reported to the NYSPI IRB and DSMP 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 & DSMP.

8.4.3 Reporting of Pregnancy

Reporting of pregnancy will be to the treating physician, PI, NYSPI IRB and DSMP. There is no ability to remove a Vivitrol injection from a pregnant participant. Although it is not desirable to maintain a pregnant participant in a PK study as hormonal changes due to pregnancy may adversely affect the PK of the IP, as Vivitrol is currently an approved medication, there are no major concerns for the participant's safety if they become pregnant. However pregnant participants will have their data after confirmed pregnancy analyzed separately in case there are changes in PK characteristics as a result of the pregnancy. Any pregnancies will also be reported to the FDA in annual progress reports.

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 PI 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 PI, or termination of a study by the Sponsor, may include but are not limited to:

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

Study termination will be reported to the PI, NYSPI IRB, DSMP 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 PI 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 section 8.6.3 for details) will meet quarterly and the *PI and study monitor will evaluate SAEs and bring them to the attention of the DSMB at the next scheduled meeting or sooner it there are significant concerns.* 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. John Rotrosen, a Professor of Psychiatry at New York University and a senior addiction pharmacotherapy researcher. Two additional faculty members from the division will join the DSMB; Dr. Elias Dakwar, an opioid dependence treatment investigator in the division, and Dr. Arthur R. Williams, another research psychiatrist in the division. In addition, two research physicians from outside of the division will join the DSMB, Dr. Jonathan Stewart, a senior investigator in the Department of Psychiatry at Columbia University and expert in mood disorder pharmacotherapy, and Dr. Sandra Springer, an infection disease specialist at Yale School of Medicine, who has extensive experience studying naltrexone use in treatment for patients with hepatitis and HIV.

The DSMB will meet before the study launch and quarterly to conduct initial and ongoing study review and review all AEs that occurred in the study. PI and study monitor will evaluate SAEs and bring them to the attention of the DSMB at the next scheduled meeting or sooner it there are significant concerns. 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 care provided to 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 subject 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

NTX (and 6βN) plasma concentration data will be explored by Non-Compartmental Analysis (NCA). Mean, median, standard deviation and coefficient of variation of parameters such as $AUC_{0\text{-}28days}$, C_{trough}, and C_{max} will be reported for each day for which the parameter is available, which is the primary objective of this study. The Accumulation Ratio (AR) of these parameters comparing the sixth with the first administration will inform us if there is accumulation of NTX (and 6βN) and if this accumulation is substantial. This is a secondary objective of this study.

Comparison of the cumulative $AUC_{0\text{-}28days}$, as well as overall C_{max} and C_{trough} during six consecutive Vivitrol administrations with previously determined 6-month data after OLANI (as determined in study GM0017) will inform us about bioequivalence of the two formulations. This is an exploratory objective of this study. Appropriate paired statistics will be used to compare the first with the sixth Vivitrol administration and to compare 6 months of Vivitrol with six months of OLANI.

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 assessed from the NTX and 6βN plasma data using PK software (Phoenix Winnonlin, Princeton, NJ) and expressed and tabulated as a mean, median, standard deviation and co-efficient of variation for each administration of Vivitrol.

Participants who submitted at least 75% valid pharmacokinetic blood samples from all study arms shall be measured for pharmacokinetic parameters of C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}28days}$ and $AUC_{0\text{-}\infty}$.

Accumulation of NTX and its metabolite is investigated using the Accumulation Ratio (AR) for $AUC_{0\text{-}28days}$, $AUC_{0\text{-}\text{-}\infty}$, C_{max} and C_{trough}. An accumulation ratio of 1 (e.g., AUC0-28days, 6^{th} administration / AUC0-28days, 1^{st} administration) indicates that there is no accumulation.

As an exploratory endpoint we will also compare the cumulative $AUC_{0\text{-}28days}$ during 6 consecutive administrations of Vivitrol with the AUC0-6months after OLANI, which was determined for each of these patients in study GM0017. In addition, C_{max} and C_{trough} will be compared for both formulations. Comparisons will be done using the ratio of the geometric mean of these parameters for each formulation.

10.4.2 Analysis of the Primary Endpoint

The pharmacokinetic parameters of C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}28days}$ and $AUC_{0\text{-}\infty}$ will be assessed from participants who submitted at least 75% valid pharmacokinetic blood samples. The data will be investigated using exploratory statistics. Means, medians, Standard

Deviations and Coefficients of Variation will be calculated for each administration and will be tabulated.

10.4.3 Analysis of the Secondary Endpoint(s)

We will calculate the Accumulation Ratio (AR) for $AUC_{0\text{-}28days}$, C_{max} and C_{trough} by comparing the parameter after one administration with the same parameter after another, e.g., $AUC_{0\text{-}28days,\ 6th\ administration}$ / $AUC_{0\text{-}28days,\ 1st\ administration}$. An AR of 1 (or a value close to 1) indicates little to no accumulation.

This analysis will be accompanied by visual inspection of the plasma concentration time curves of NTX and its metabolite, which will be plotted graphically. The visual inspections and comparisons of the curves are exploratory endpoints of this study.

Visual inspection of the curves will also inform us if the plasma concentration time profile after the first administration is similar to that after the sixth administration of Vivitrol.

Visual inspection of the Vivitrol curves and comparison with the visual inspection of the OLANI (as determined in GM0017) curves in the same patients might also inform us if earlier identified rapid metabolizers of the OLANI formulation are also rapid metabolizers of the Vivitrol formulation.

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, SAEs, adverse drug reactions (ADR), and suspected unexpected serious AE will be recorded. Additionally, counts of the number of laboratory values that fall outside of the normal range will be used to assess safety.

10.4.5 Adverse Events

After coding of AEs according to the Medical Dictionary for Regulatory Activity classification (MedDRA) and assignment to a system organ class and preferred term, all AEs recorded during the course of the trial will be listed by the participant number.

An AE will be considered as 'treatment emergent' if it occurred after the first drug administration of each period or if it was present prior to drug administration but exacerbated after the drug administration. All other adverse events will be considered “pre-treatment.”

In the case where it is not possible to define an AE as being treatment emergent or not, the AE will be classified as treatment emergent as the most conservative approach.

A summary table describing all the TEAEs occurring during the trial will be produced overall and by treatment sequence using frequency of events and number and percentage of subjects experiencing these events. In addition, all TEAEs will be tabulated by intensity and relationship to drug in the same manner. Multiple occurrences of the same TEAE in one participant during the same treatment in the trial will be counted as multiple events in the frequency counts for adverse events. If a participant experiences more than one occurrence of the same TEAE during the same treatment in the trial, the participant will only be counted once using the worst severity and the strongest relationship.

All adverse events leading to trial or treatment discontinuation will be listed by treatment sequence and participant.

All SAEs will be listed by treatment sequence and participant.

10.4.6 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.

10.4.7 Baseline Descriptive Statistics

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

10.4.8 Planned Interim Analyses

10.4.8.1 Safety Review

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

10.4.8.2 Efficacy Review

No interim efficacy analysis will be performed.

10.4.9 Additional Sub-Group Analyses

No sub-group analysis will be performed.

10.4.10 Multiple Comparison/ Multiplicity

No adjustment will be made for multiple comparisons.

10.4.11 Tabulation of Individual Response Data

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

10.4.12 Exploratory Analyses

No exploratory analysis will be conducted.

10.5 SAMPLE SIZE

At the completion of the study, it is desirable that a minimum of 12 participants will complete a minimum of 75% blood collection time points.

10.6 SOFTWARE

PK parameters are determined using Non-Compartmental Analysis embedded within Phoenix WinNonlin Pharmacokinetics software (Certara, Princeton, NJ).

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., GLP & 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 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[24] and the Declaration of Helsinki[25].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 Consent (PIC) describing the study and providing sufficient information so that they are able to make an informed decision about their participation in the trial. The PIC form will be submitted with the research application for review and approval by the IRB.

13.3.2 Consent Procedures and Documentation

The PI (or authorized designee) will ensure that the participant 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 PIC 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 PIC 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 Authority Log 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.

13.4.1 Research Use of Stored Human Samples, Specimens or Data

13.4.1.1 Naltrexone bloods

All NTX blood samples will be collected in 1 x 10 mL Na Heparin tubes (9 mL) and stored in the study site refrigerator at 0-4°C until specimen preparation.

Specimen preparation will be carried out at study site within 24 hours. This will involve centrifugation of the blood sample to enable plasma separation. Plasma will be extracted and stored in suitable containers (1.5 mL Eppendorf's) and stored at -80°C. When batches of greater than 50 samples are available these can then be shipped on dry ice to Xenobiotic Laboratories for analysis. Backup samples will remain stored at Clinilabs for the duration of the trial. All samples will be analyzed for free (unconjugated) NTX and free (unconjugated) 6βN quantification. It is anticipated that samples will be prepared and split into 4 aliquots, with 2 being used for analysis and 2 serving as a backup being stored de-identified in a -80°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 study site, as per the site's 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 study personnel. An eCRF will be completed for each participant.

A confidential list of participant names, contact details, and screening numbers will be kept by the study site. 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 PI 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 PI, or the study site staff. 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 (e.g., FDA).

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 the PI, Clinilabs, and additional study personnel from NYSPI. A Clinical Pharmacology 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 Clinilabs Responsible Clinician Dr. Maha Ahmad, the Sponsor Representative, and site 1 representative Dr. Edward Nunes (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
N/A	0.1	N/A. New document that was submitted in a Meeting Package to the FDA. This version was never implemented.
01 October 2020	0.2	Reduced the scope of the protocol to focus only on Vivitrol assessments in a small number of participants completing study GM 0017.
27 October 2020	0.3	Updated to incorporate changes requested by the FDA.
17 December 2020	0.4	Updated to incorporate changes requested by the reviewing IRB and those made by the study team during development of the database.
25 March 2021	0.5	The primary reason for this amendment is to expand the number of participants. Enrollment of at least 15 participants will provide more PK data and funding is now available to support this larger N.

18 SUMMARY OF CHANGES FROM PREVIOUS VERSION

18.1 Version 0.2

Affected Section(s)	Summary of Revisions Made	Rationale
Multiple	Reduced the scope of the protocol throughout to focus only on Vivitrol assessments in a small number of participants completing study GM 0017.	To gather crossover Vivitrol data in participants who have completed their OLANI dosing.

18.2 Version 0.3

Affected Section(s)	Summary of Revisions Made	Rationale
Section 7.3.4.1 and Table 7-1	Inclusion of a pregnancy test on Admission Day 0.	Added in response to request from the FDA.
Section 2.3.1	Inclusion of Vivitrol 'Warnings and Precautions' from Section 5 of the US prescribing information into Section 2.3.1 of the protocol.	Added in response to request from the FDA.

18.3 Version 0.4

Affected Section(s)	Summary of Revisions Made	Rationale
Section 5.4.2.1	Old Text: This would include a participant who becomes suicidal, or a participant who goes on drug binges (including non-opiate drugs). New Text: This would include a participant who becomes suicidal, or a participant who goes on ~~severe~~ drug binges ~~endangering him/herself~~ (including non-opiate drugs).	IBR requested change to enhance participant safety (i.e. any binge alone will be sufficient for discontinuation).

Affected Section(s)	Summary of Revisions Made	Rationale
Section 7.1.1.2	Study clinician" has been replaced with study-trained medical professional (e.g., such as physicians or physician assistants).	Change resulted from IRB review and delineates that other staff, besides the study clinician/ PI, has been medically trained by the study PI to consent participants to the study and provide them with all necessary medical information. Participants will always have opportunity to discuss all relevant information with the study PI
Section 7.3.1	Screening visits 1 and 2 have been combined.	Change made by the study team during development of the database. There will be no duplicate assessments.
Section 7.3.3.1 Section 7.3.3.5 Section 7.3.4, Section 7.3.5	The General Health Questionnaire and Michigan Health Outcomes Questionnaire were replaced with the Patient Health Questionnaire (PHQ) and the Beck Depression-II (BDI-II).	Change made by the study team during development of the database.
Section 7.3.9	Changes described above have been incorporated into Table 7-1 along with additional clarifications.	IRB review and changes made by the study team during development of the database.
Section 7.4	Made language and time frame more specific.	Change made by the study team during development of the database.
Section 7.9	Total compensation for the study has been changed from $4,630 to $4,580.	Revision made to reflect the change from 2 screening visits down to 1 screening visit.
Section 13.3.2	Removed 'or the participant's legal representative' from the text.	Change resulted from IRB review since participants must have their own capacity to consent.

18.4 Version 0.5

Affected Section(s)	Summary of Revisions Made	Rationale
Section III	Sponsor signature page added.	To document Sponsor approval of the protocol.
Protocol Summary (Section V) & Section 2.2	Insertion - Note: In the future, an expansion of this protocol is planned in order to include additional participants that initially receive 2 doses of Vivitrol followed by the OLANI treatment (i.e. the 'cross-over' group). This expansion may occur under this same protocol ID or a new protocol ID.	Clarification of future plans for drug development.
Protocol Summary & Section 5.1	Old Text: Men or women between ≥18 and <57 years old Without DSM 5 – Substance Related Disorders classification; in sustained remission is not exclusionary New Text: Men or women aged at least 18 (≥18) and no older than 57 (<58), without DSM 5 - Substance Related Disorders classification; in sustained remission is not exclusionary	Clarification made regarding eligibility criteria for age.
Section 5.1	Deletion of "A NTX blood sample will be taken at baseline to confirm zero NTX levels (<0.1 ng/mL) for data analysis."	This sampling is still occurring and is covered in Section 7.3.1 and Table 7-1 but is not a part of 'eligibility' for this version of the protocol since participants have already received OLANI.
Section 4.1, Section 5.3.1 & Section 10.5	Sample size increased from 6 participants to 'up to 15' participants with 12 participants expected to complete the study.	This is the primary reason for this amendment: to expand the number of participants. Enrollment of at least 15 participants is more appropriate. It will provide more PK data and funding is now available to support this larger N.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 7.2.2.1, Section 7.2.4.1, & Section 13.4.1.1	Changed from '2 x 4.5 mL' tubes to '1 x 10 mL' tubes	Changed to reflect the actual tubes being utilized.
Table 7-1	Updated the 'Unscheduled visit' row to 'Unscheduled/Late visit' row	Clarification
Section 8.4	Updated section to specify that the PI and study monitor will evaluate SAEs, and unexpected AEs in real time. They will bring these concerns to the DSMB at the next scheduled meeting or sooner if there are significant concerns.	This plan was agreed at the most recent DSMB meeting.
Global	Other minor changes were made to correct spelling, grammar, or formatting issues which do not change any meaning to the text.	Clarification and correction

19 LITERATURE REFERENCES

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