

**A Prospective, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial  
Of Bupropion Hydrochloride Sustained-Release In The Treatment Of Sexual  
Dysfunction In Men On Methadone Maintenance Therapy.**

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**Study Product :** Bupropion Hydrochloride Sustained-Release

**Protocol Number :** AY001

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**LIST OF ABBREVIATIONS**

|                                |   |
|--------------------------------|---|
| AE                             | Adverse effect  |
| b.d                            | Twice per day   |
| CGI-SF                         | Clinical Global Impression Scale adapted for Sexual Function  |
| ECG                            | Electrocardiogram   |
| HIV                            | Human immunodeficiency virus                                  |
| IIEF-15                        | International Index of Erectile Function                      |
| ITT                            | Intention-to-treat analyses                                   |
| MADRS, Malay                   | Montgomery-Åsberg Depression Rating Scale                     |
| M.I.N.I                        | Mini International Neuropsychiatric Interview                 |
| OTI                            | Opiate Treatment Index  |
| WHOQoL-Brief,<br>Malay version | World health organization Quality of Life-Brief Scale         |
| Mal-GRIMS                      | Malay Version of the Golombok-Rust Inventory of Marital State |
| SAE                            | Serious Adverse Experiences                                   |

## PROTOCOL SUMMARY

|  |  |
|--|--|
| <b>TITLE</b>   | Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial Of Bupropion Hydrochloride Sustained Release In The Treatment Of Sexual Dysfunction In Men On Methadone Maintenance Therapy.  |
| <b>SHORT TITLE</b>   | RCT Bupropion SR in SD among MMT men   |
| <b>INVESTIGATOR</b>  | Yee Hway Ann @ Anne Yee  |
| <b>SYUDY PROTOCOL</b>  | AY001  |
| <b>Phase</b>   | Phase II   |
| <b>Study Center(s)</b>   | Single-center (University Malaya Medical Centre)   |
| <b>STUDY DESIGN</b>  | Randomized, Double-Blind, Placebo-Controlled Study.  |
| <b>OBJECTIVE</b>   | To assess the therapeutic effect of bupropion hydrochloride sustained-release in the treatment of sexual dysfunction in men on methadone maintenance therapy   |
| <b>NUMBER OF SUBJECTS</b>                                      | 70 (35 for each arm)   |
| <b>Diagnosis and Main Inclusion Criteria</b>                   | Adult had a diagnosis of opioid dependence base on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, who were experiencing constant sexual dysfunction for $\geq 4$ weeks while taking a stable dose of methadone for $\geq 6$ months.            |
| <b>TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION</b>         | Bupropion hydrochloride sustained-release (Wellbutrin SR) 150mg once a day for 7 days then 150mg twice a day for 35 days. Taken orally by the subjects.  |
| <b>DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY</b> | Subjects will be on study for up to 63 days<br>Screening: up to 7 days(1 week)<br>Treatment: 42days (6 weeks)<br>Follow-up: 14 days (2 weeks)<br>The total duration of the study is expected to be 24 months. 20months for subject recruitment and 4 months for final subject follow-up. |
| <b>EFFICACY EVALUATIONS</b>                                    |  |
| <b>PRIMARY ENDPOINT</b>  | <ul style="list-style-type: none"> <li>Change from baseline International Index of Erectile Function (IIEF-15) score.</li> </ul>   |
| <b>SECONDARY ENDPOINTS</b>                                     | <ul style="list-style-type: none"> <li>Mean improvement in scores on the Clinical Global Impression Scale adapted for sexual Function (CGI-SF)</li> <li>Mean improvement in scores on the Arizona Sexual Experience</li> </ul>   |

|   |  |
|---|--|
|   | Scale (ASEX) <ul style="list-style-type: none"> <li>• Safety and Tolerability</li> </ul>   |
| <b>OTHER EVALUATIONS</b>                    | <ul style="list-style-type: none"> <li>• Montgomery-Åsberg Depression Rating Scale (MADRS- Malay version )</li> <li>• Mini International Neuropsychiatric Interview (M.I.N.I),</li> <li>• Opiate Treatment Index (OTI)</li> <li>• World health organization Quality of Life-Brief Scale (WHOQoL-Brief, Malay version) ,</li> <li>• Malay Version of the Golombok-Rust Inventory of Marital State (Mal-GRIMS)</li> <li>• Rapid urine drug test</li> </ul> |
| <b>SAFETY EVALUATIONS</b>                   | Incidence of adverse events  |
| <b>STATISTICS<br/>Primary Analysis Plan</b> | Data will be analyzed using linear mixed-effects model.  |

|   |           |
|---|-----------|
| <b>TABLE OF CONTENTS</b>  | <b>Pg</b> |
| <b>LIST OF ABBREVIATIONS</b>                                    | 3         |
| <b>PROTOCOL SUMMARY</b>   | 4         |
| <b>INTRODUCTION</b>   | 9         |
| <b>1. BACKGROUND</b>  | 9         |
| <b>1.1 Investigational Agent</b>                                | 10        |
| <b>1.2 Overview of Non-Clinical Studies</b>                     | 10        |
| <b>1.3 Overview of Clinical Studies</b>                         | 11        |
| <b>1.4 Risk / Benefit Assessment</b>                            | 11        |
| 1.4.1 Dose Rationale  | 11        |
| 1.4.2 Potential Risk  | 11        |
| 1.4.3 Potential Benefit   | 11        |
| 1.4.4 Risk Benefit Ratio  | 11        |
| <b>2 STUDY RATIONALE</b>  | 12        |
| <b>3 STUDY OBJECTIVES</b>                                       | 12        |
| <b>3.1 Primary Objective</b>                                    | 12        |
| <b>3.2 Secondary Objectives</b>                                 | 12        |
| <b>4 STUDY DESIGN</b>   | 13        |
| <b>4.1 Design</b>   | 13        |
| <b>4.2 Procedure</b>  | 13        |
| <b>4.3 Project Timetable</b>                                    | 14        |
| <b>5 CRITERIA FOR EVALUATION</b>                                | 14        |
| <b>5.1 Primary Efficacy Endpoint</b>                            | 14        |
| <b>5.2 Secondary Efficacy Endpoints</b>                         | 14        |
| <b>5.3 Safety Evaluations</b>                                   | 14        |
| <b>6 SUBJECT SELECTION</b>                                      | 15        |
| <b>6.1 Study Population</b>                                     | 15        |
| <b>6.2 Inclusion Criteria</b>                                   | 15        |
| <b>6.3 Exclusion Criteria</b>                                   | 15        |
| <b>6.4 Subject Recruitment and Screening</b>                    | 15        |
| <b>7 EARLY WITHDRAWAL OF SUBJECTS</b>                           | 16        |
| <b>7.1 When and How to Withdraw Subjects</b>                    | 16        |
| <b>7.2 Data Collection and Follow-up for Withdrawn Subjects</b> | 17        |
| <b>8 STUDY TREATMENTS</b>                                       | 17        |
| <b>8.1 Method of Assigning Subjects to Treatment Groups</b>     | 17        |
| <b>8.2 Blinding</b>   | 17        |

|             |   |    |
|-------------|---|----|
| <b>8.3</b>  | <b>Formulation of Test and Control Products</b>     | 18 |
| 8.3.1       | Description   | 18 |
| 8.3.2       | Treatment Regimen                                   | 18 |
| 8.3.2.1     | Route   | 18 |
| 8.3.2.2     | Regime  | 18 |
| <b>8.4</b>  | <b>Preparation and Administration of Study Drug</b> | 18 |
| <b>8.5</b>  | <b>Prior and Concomitant Therapy</b>                | 18 |
| <b>8.6</b>  | <b>Packaging and Labeling</b>                       | 18 |
| <b>8.7</b>  | <b>Receiving, Storage, Dispensing and Return</b>    | 19 |
| 8.7.1       | Receipt of Drug Supplies                            | 19 |
| 8.7.2       | Storage   | 19 |
| 8.7.3       | Dispensing of Study Drug                            | 19 |
| 8.7.4       | Return or Destruction of Study Drug                 | 19 |
| <b>8.8</b>  | <b>Measures of Treatment Compliance</b>             | 19 |
| <b>9</b>    | <b>STUDY PROCEDURES AND GUIDELINES</b>              | 19 |
| <b>9.1</b>  | <b>Clinical Assessments</b>                         | 20 |
| 9.1.1       | Concomitant Medications                             | 20 |
| 9.1.2       | Demographics  | 20 |
| 9.1.3       | Medical History                                     | 20 |
| 9.1.4       | Physical Examination                                | 20 |
| 9.1.5       | Adverse Events                                      | 20 |
| <b>9.2</b>  | <b>Clinical Laboratory Measurements</b>             | 20 |
| 9.2.1       | Blood investigation                                 | 20 |
| 9.2.2       | Urinalysis  | 20 |
| <b>10</b>   | <b>EVALUATIONS BY VISIT</b>                         | 21 |
| <b>10.1</b> | <b>Visit 0(Screening visit and Randomization)</b>   | 21 |
| <b>10.2</b> | <b>Visit 1 (week 1)</b>                             | 21 |
| <b>10.3</b> | <b>Visit 2 (week 2)</b>                             | 21 |
| <b>10.4</b> | <b>Visit 3 (week 3)</b>                             | 21 |
| <b>10.5</b> | <b>Visit 4 (week 4)</b>                             | 22 |
| <b>10.6</b> | <b>Visit 5 (week 5)</b>                             | 22 |
| <b>10.7</b> | <b>Visit 6 (week 6) (end of study drug)</b>         | 22 |
| <b>10.8</b> | <b>Early Withdrawal Visit</b>                       | 22 |

|           |   |           |
|-----------|---|-----------|
| <b>11</b> | <b>STATISTICAL PLAN</b>                               | <b>22</b> |
| 11.1      | Sample Size Determination                             | 22        |
| 11.2      | Statistical Methods                                   | 22        |
| 11.3      | Subject Population(s) for Analysis                    | 23        |
| 11.4      | Data Management                                       | 23        |
| <b>12</b> | <b>ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION</b> | <b>23</b> |
| 12.1      | Adverse Events  | 23        |
| 12.2      | Serious Adverse Experiences (SAE)                     | 25        |
| <b>13</b> | <b>DISCONTINUATION AND REPLACEMENT OF SUBJECTS</b>    | <b>28</b> |
| 13.1      | Early Discontinuation of Study Drug                   | 28        |
| 13.2      | Withdrawal of Subjects from the Study                 | 29        |
| <b>14</b> | <b>PROTOCOL VIOLATIONS</b>                            | <b>29</b> |
| <b>15</b> | <b>DATA COLLECTION, RETENTION AND MONITORING</b>      | <b>30</b> |
| 15.1      | Confidentiality                                       | 30        |
| 15.2      | Source Documents                                      | 30        |
| 15.3      | Data Quality Control and Reporting                    | 30        |
| 15.4      | Records Retention                                     | 30        |
| <b>16</b> | <b>STUDY MONITORING, AUDITING, AND INSPECTING</b>     | <b>30</b> |
| 16.1      | Study Monitoring Plan                                 | 30        |
| 16.2      | Auditing and Inspecting                               | 30        |
| <b>17</b> | <b>ETHICAL CONSIDERATIONS</b>                         | <b>31</b> |
| 17.1      | Informed Consent Form                                 | 31        |
| <b>18</b> | <b>STUDY FINANCES</b>                                 | <b>31</b> |
| 18.1      | Funding Source  | 31        |
| 18.2      | Conflict of Interest                                  | 32        |
| <b>19</b> | <b>PUBLICATION PLAN</b>                               | <b>32</b> |
|           | <b>APPENDIX 1</b>                                     | <b>33</b> |
| <b>20</b> | <b>REFERENCES</b>                                     | <b>34</b> |
| <b>21</b> | <b>ATTACHMENTS</b>                                    | <b>35</b> |



## INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to the international standards of Good Clinical Practice (International Conference on Harmonization guidelines), applicable government regulations and University Malaya Medical Centre research policies and procedures.

### 1. BACKGROUND

Sexual dysfunctions, such as reduced libido or arousal and impairments in erectile, ejaculatory and orgasmic functions, are commonly found in men among both the mentally ill as well as the healthy populations. The prevalence of sexual dysfunction among healthy men ranges from 20% to 35%, and in male populations with psychiatric illness, 50% to 65%. [1-5]

Methadone maintenance treatment (MMT) is a comprehensive treatment program that involves the long-term prescribing of methadone as a substitution therapy for opioid dependence. Despite the effectiveness of the methadone maintenance therapy[6], the meta-analytical pooled prevalence for sexual dysfunction among methadone users was 52% (95% confidence interval [CI], 0.39–0.65). In this meta-analysis, hypoactive sexual desire and low libido were the most prevalent sexual dysfunctions compared to other sexual dysfunction, accounting for 51%[7]. Methadone-maintained patients, their partners and clinicians who were interviewed regarding the influence of sexual dysfunction perceived that that sexual dysfunction decreased quality of patient's sexual life [8] and damaged intimate relationships, while at the same time possibly increasing risk of dropout from methadone maintenance therapy prematurely [9] and to use suboptimal methadone dose or other illicit drugs. [10] Management for methadone induced sexual dysfunction remain a challenge for the physicians because the reducing or stopping the methadone in this group of patients may not be always possible. Hence, the physicians need other strategies to manage the sexual dysfunction in this group of patients.

Methadone is the slow-and-long acting opiate agonist that cause the stimulation of mu opiate receptors in the various area of the brain. There are few hypothesis that try to explain the correlation of methadone and sexual dysfunction. One of well known hypothesis was the neuroendocrinologic effects of methadone that exert on the tubero-infundibular and hypothalamus-pituitary-gonadal (HPG) axis. The previous studies found that the patients in methadone therapy had alternation of the prolactin levels compared with the healthy subjects. Hence, the hypothesis that the chronic stimulation of the  $\mu$  opiate receptors by methadone, alters the functioning of the tubero-infundibular axis and the dopaminergic control of prolactin with the consequential impact on sexual functioning was formulated. [11] A high level of circulating prolactin causes inhibition of gonadotrophin releasing hormone which lowers levels of sex hormone, especially testosterone. Men with low testosterone levels may exhibit a decrease in sexual interest.[12]This is evidenced by aquantitative meta-analysis study, which showed that testosterone, free testosterone and estradiol level was impaired and statistically associated with sexual dysfunction in the patients who were on methadone maintenance therapy.[13] However, in a recent study also showed that there were more than 50% of methadone maintenace therapy patients had sexual dysfunction ( 55% had erectile dysfunction and

65% had orgasm dysfunction), only 15% of them had hyperprolactinaemia.[14] Therefore, this hypothesis could not solely explain the sexual dysfunction in this group of patients.

The effects of the neurotransmitter dopamine on male sexual behavior have been discussed for centuries. The mesoaccumbens dopamine system has been implicated in the neural processes of sexual motivation in many animal studies.[15] However, the first recognized dopamine-mediated enhancement of sexual behavior in human was when administration of l-dopa (3,4-dihydroxy-l-phenylalanine), the precursor to dopamine, to men suffering from Parkinson's disease resulted in increased libido and sexual potency. [16] In a recent imaging study showed that the methadone maintenance patients has reduced dopamine receptor 2 (D2) in the various part of the brain with the consequences of reduced functioning of the dopaminergic system in brain.[17] There are studies also showed methadone inhibit copulatory behaviour when given either acutely or chronically in animals and decrease socio-sexual interaction, apparently without interfering with locomotion.[18] Therefore, there are researchers proposed to use dopamine agonist such as bromocriptine or dopamine reuptake inhibitor such as bupropion to treat sexual dysfunction in this group patients. There was an open-labelled, quasi-experimental study done by Tatari et al. In 2013 [19], whereby 100mg of Bupropion was administered on 67 methadone maintenance men who had erectile dysfunction for six weeks. In this study, Bupropion significantly improved the erectile function in this group of patients. However, the sample size of that study was small and with many methodological limitations. Hence, I aim to conduct a randomised controlled trial of Bupropion in the treatment of erectile dysfunction among men on methadone maintenance therapy

## 1.1 Investigational Agent

Bupropion hydrochloride sustained-release (Trade name is Wellbutrin SR™), an antidepressant of the aminoketone class, is an inhibitor of the neuronal reuptake of norepinephrine and dopamine, and does not inhibit the reuptake of serotonin. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is C<sub>13</sub>H<sub>18</sub>ClNO•HCl.[20]

Bupropion is extensively metabolized in humans. Three metabolites are active: hydroxybupropion, which is formed via hydroxylation of the tert-butyl group of bupropion, and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. The elimination half-life of metabolites are ranged from 20 hours to 37 hours. [20]

## 1.2 Overview of Non-Clinical Studies

**Carcinogenesis** : Nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m<sup>2</sup> basis) was found in a rat study but not in the mouse study. There were no increase in malignant tumors of the liver and other organs were seen in either study. Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity assay.

Bupropion produced an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.[20]

A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.[20]

### 1.3 Overview of Clinical Studies

There was an open-labelled, quasi-experimental study done by Tatari et al. In 2013 [19], whereby 100mg of Bupropion was administered on 67 methadone maintenance men who had erectile dysfunction for six weeks. In this study, Bupropion significantly improved the erectile function in this group of patients (IIEF score improved from  $12.79 \pm 1.37$  to  $15.94 \pm 2.14$ ). However, the sample size of that study was small and with many methodological limitations.

### 1.4 Risk / Benefit Assessment

#### 1.4.1 Dose Rationale

In this study, the usual adult target dose for bupropion hydrochloride sustained-release is 300 mg per day, given as 150 mg twice daily. Initiate dosing with 150 mg per day given as a single daily dose in the morning. After 3 days of dosing, the dose may be increased to the 300-mg-per-day target dose, given as 150 mg twice daily. This is based on a phase II, randomized, placebo controlled, adjunctive bupropion sustained-release (SR) on male sexual dysfunction (SD) induced by a selective serotonin reuptake inhibitor. In this study, 117 patients were randomly assigned to receive 12 weeks of bupropion SR 150 mg twice daily. 97.3% of the patients did not complain any adverse effects (AEs), the most commonly reported AEs were headache (8.5%), nasopharyngitis (6.8%), insomnia (6.0%) and dry mouth (6.0%). There were no severe AEs during the trial.[20]

#### 1.4.2 Potential Risk

The potential risks of this study include adverse reactions to bupropion hydrochloride sustained-release. Clinical condition of the subjects will be closely monitored by the study design

#### 1.4.3 Potential Benefit

Methadone induced sexual dysfunction that is experienced by the patients who are receiving study medication may be improved. Patients in the study will receive close psychiatric and medical attention. The potential benefits to the partners include improvement of the marital relationship with the patients

#### 1.4.4 Risk Benefit Ratio

The potential benefits of this study far outweigh the potential risks. Methadone induced sexual dysfunction in this group of patients by far does not have standard treatment. Literature reviews have shown that the lowering or stopping the methadone dosage increase the relapse risk in this group of patients. In contrast, bupropion as an adjunctive treatment was shown to have early positive effect on the treatment of erectile dysfunction in this group of patients. Patients accepted into the study will receive close medical and

psychiatric monitoring as well as treatment with methylphenidate that has a well-documented safety profile. Patients will be screened prior to admission into the study. The subjects selected for participation will be monitored closely for adverse effects.

## **2 STUDY RATIONALE**

Sexual dysfunction is highly prevalent among methadone maintenance male patients. Previous studies found that sexual dysfunction decreased quality of patient's sexual life [8] and damaged intimate relationships, while at the same time increased the risk of dropout from methadone maintenance therapy prematurely [9]. Although the sexual dysfunction is related to the methadone dose, some of the ex-opioid dependent patients relapsed after their methadone dosage became too low. Worse still, some of them used other illicit drugs, especially stimulants, to boost up their sex function [10]. Currently, there are no standard treatment to treat methadone induced sexual dysfunction. Therefore, we are using bupropion hydrochloride sustained-release to treat methadone induced sexual dysfunction.

## **3 STUDY OBJECTIVES**

### **3.1 Primary Objective**

- 3.1.1** To assess the clinical efficacy of bupropion hydrochloride sustained-release in the treatment of sexual dysfunction in men on methadone maintenance therapy.

#### Hypothesis

Bupropion hydrochloride sustained-release treated subjects will show significant improvement in Clinical Global Impression Scale adapted for Sexual Function (CGI-SF) then placebo treated subjects between baseline and week 6.

### **3.2 Secondary Objectives**

- 3.2.1** To assess the clinical efficacy of bupropion hydrochloride sustained-release in the treatment of erectile dysfunction in men on methadone maintenance therapy.

#### Hypothesis

Bupropion hydrochloride sustained-release treated subjects will show significant improvement in erectile function domain in International Index of Erectile Function (IIEF-15) and Arizona Sexual Experience Scale (ASEX) then placebo treated subjects between baseline and week 6.

- 3.2.2** To assess the clinical efficacy of bupropion hydrochloride sustained-release in the treatment of intercourse dissatisfaction in men on methadone maintenance therapy.

Hypothesis

Bupropion hydrochloride sustained-release treated subjects will show significant improvement in intercourse satisfaction domain in International Index of Erectile Function (IIEF-15) then placebo treated subjects between baseline and week 6.

- 3.2.3** To assess the clinical efficacy of bupropion hydrochloride sustained-release in the treatment of orgasmic dysfunction in men on methadone maintenance therapy.

Hypothesis

Bupropion hydrochloride sustained-release treated subjects will show significant improvement in orgasmic function domain in International Index of Erectile Function (IIEF-15) then placebo treated subjects between baseline and week 6.

- 3.2.4** To assess the clinical efficacy of bupropion hydrochloride sustained-release in the treatment of hypoactive sexual desire in men on methadone maintenance therapy.

Hypothesis

Bupropion hydrochloride sustained-release treated subjects will show significant improvement in sexual desire domain in International Index of Erectile Function (IIEF-15) then placebo treated subjects between baseline and week 6

- 3.2.5** To assess the clinical efficacy of bupropion hydrochloride sustained-release in the treatment of overall dysfunction in men on methadone maintenance therapy.

Hypothesis

Bupropion hydrochloride sustained-release treated subjects will show significant improvement in overall satisfaction domain in International Index of Erectile Function (IIEF-15) then placebo treated subjects between baseline and week 6

## **4 STUDY DESIGN**

### **4.1 Design**

This is a single center, phase II, randomized, double-blind, parallel-group, placebo-controlled trial

### **4.2 Procedure**

All the male subjects who attended the methadone maintenance clinic will be approached. Screening data will be reviewed to determine subject eligibility. Subjects who meet all

inclusion criteria and none of the exclusion criteria will be entered into the study. Sexual dysfunction will be measured by CGI-SF, IIEF-15 and ASEX,

Seventy (70) of subjects will be randomized to one of two experimental treatments (35 subjects per group): bupropion hydrochloride sustained or placebo. Bupropion hydrochloride sustained or placebo will be initiated after screening and continued for 42 days of outpatient treatment. Efficacy will be take place at baseline, day 14(week 2), day 28(week four) and day 42 (week 6).

At the end of the 42 days, the continuation of treatment will be depends on the investigator's clinical judgment and End of Medication Evaluation will be perform. Every effort will be made to continue to evaluate all subjects who are randomized even if they decide to discontinue the medication.

### **4.3 Project Timetable**

The project will take 2 years. The plan is to randomize 1 subject per week, taking about 18 months to acquire 70 subjects. Follow-up evaluations will be completed 2 year from the start of the project.

## **5 CRITERIA FOR EVALUATION**

### **5.1 Primary Efficacy Endpoint**

The primary endpoint to be measured in this study is:

- CGI-SF at the baseline, day 14(week 2), day 28(week four) and day 42 (week 6).

### **5.2 Secondary Efficacy Endpoints**

- Erectile function (EF, questions 1–5 and 15) of IIEF-15 at the baseline, day 14(week 2), day 28(week four) and day 42 (week 6).
- Intercourse satisfaction (questions 6–8) of IIEF-15 at the baseline, day 14(week 2), day 28(week four) and day 42 (week 6).
- Orgasmic function (questions 9 and 10) of IIEF-15 at the baseline, day 14(week 2), day 28(week four) and day 42 (week 6).
- Sexual desire (questions 11 and 12) of IIEF-15 at the baseline, day 14(week 2), day 28(week four) and day 42 (week 6).
- Overall satisfaction (questions 13 and 14) of IIEF-15 at the baseline, day 14(week 2), day 28(week four) and day 42 (week 6).
- ASEX at the baseline, day 14(week 2), day 28(week four) and day 42 (week 6).

### **5.3 Safety Evaluations**

- The primary safety endpoint will be measurement and collection of any serious adverse event that occurs from initial study treatment through and including 28 days after cessation of study treatment.

## 6 SUBJECT SELECTION

### 6.1 Study Population

Subjects with a diagnosis of opioid dependence base on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria who meet the inclusion and exclusion criteria will be eligible for participation in this study.

### 6.2 Inclusion Criteria

- Patients were eligible if they were aged 18–60 years
- Had a diagnosis of opioid dependence base on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria
- While taking a stable dose of methadone In UMMC (University Malaya Medical Centre) and University Malaya centre of Addiction Science (UMCAS) outpatient clinic for  $\geq 6$  months
- Were experiencing constant sexual dysfunction for  $\geq 4$  weeks
- Were in a stable sexual relationship with a female partner for  $\geq 6$  months

### 6.3 Exclusion Criteria

- Severe behavior disturbances or psychotic symptoms
- Obvious organic illnesses caused the sexual dysfunction (such as diabetics or patients with heart and vascular disease)
- Those with history of sexual dysfunction before methadone therapy
- Receiving antiviral treatment for viral hepatitis or HIV, or androgen replacement treatment.
- History of an eating disorder (eg, anorexia, bulimia) or seizures (eg, epilepsy)
- Using other psychotropic medications other than methadone
- Clinically significant abnormal laboratory values.
- Clinically significant abnormal ECG.  
Documented history of other psychiatric diagnosis (schizophrenia, bipolar disorder, organic brain disorder, dementia etc.)
- Refused to give participate.

### 6.4 Subject Recruitment and Screening

Subjects are identified from the In UMMC (University Malaya Medical Centre) and University Malaya centre of Addiction Science (UMCAS) outpatient clinic. Subjects will undergo an informed consent process in accordance with GCP (see section 11 Ethical

Considerations). To qualify for the study, subjects must meet all inclusion and none of the exclusion criteria as determined by pre-treatment battery measures.

#### Laboratory and physical exam screening

These include a complete medical history and physical exam; vital signs and weight; baseline ECG (12-lead); routine blood work (study laboratory tests) including renal function test, Liver function test, fasting lipid profile, fasting blood sugar, total testosterone (TT), free testosterone (FT), estradiol (E2), luteinizing hormone (LH), and prolactin.), urinalysis (U/A) for opioid (non methadone), marijuana, methamphetamine and ecstasy. Study laboratory tests are specifically listed with normal cutoff values in Attachment.

#### Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and scales measurement

A M.I.N.I will be administered to rule out other psychiatric disorders. All medications taken by the patient for the 30 days prior to screening will be documented. They will complete the MADRS, Malay version , OTI, WHOQoL-Brief, Malay version and Mal-GRIMS.

The efficacy between the groups is assessed and compared using the measurement of CGI-SF, IIEF15 and the 5 domain, and ASEX

#### Documentation of Screening

Screening assessments will be performed to determine subject eligibility criteria, which will be documented on a case report form. The PI will confirm and sign off on the inclusion and exclusion criteria on a case report form (CRF) prior to the patient formally included in the study or given study medication.

## **7 EARLY WITHDRAWAL OF SUBJECTS**

### **7.1 When and How to Withdraw Subjects**

Subjects will be withdrawn from the study in the following condition:

- Report of clinical significant adverse events felt to be related to study drug
- Failure of subject to adhere to protocol requirements
- Subject withdraw consent or their authorization to use their protected health information
- Subject is too ill to continue with the study procedure
- Deemed by the principal investigator to be in their best interest

Subjects discontinued from the clinical trial will be scheduled for a final evaluation. The investigator or sub-investigators will continue the care, consider alternative treatment or given appropriate treatment referrals for the subjects who withdraw from the study.



All subjects randomized into the study will be included in the final study analyses. Subjects are not dropped from all study activity unless they request not to be contacted or cannot be located for follow-up assessment. Subjects will be informed at the consent session that treatment may be discontinued due to:

- Intolerable side effects;
- Significantly abnormal laboratory values or confirmed with a repeat testing;
- Development or exacerbation of sexual dysfunction;
- Clinical deterioration for any reason or any clinical status that necessitates IP admission;

Reasons why subjects are discontinued from the clinical trial will be documented on the Study Termination Form, along with any referrals that are made. A final safety evaluation will be conducted as soon as possible on all randomized subjects who are discontinued. Every effort will be made to continue to collect data on every randomized subject for the entire study duration regardless of whether or not the subject continues to take study medication, assuming the subject has now withdrawn his/her authorization to obtain such information.

## **7.2 Data Collection and Follow-up for Withdrawn Subjects**

Even though subjects may be withdrawn prematurely from the study all adverse event data will continue to be collected through 14 days from cessation of study drug (with the subject's permission). Subjects who have study drug discontinued for any reason, but are willing to complete study visits will have all assessments administered and collected. For the final measures, subjects will receive all assessments that were scheduled for the End of Study visit.

# **8 STUDY TREATMENTS**

## **8.1 Method of Assigning Subjects to Treatment Groups**

Up to 70 eligible patients will be randomly assigned to Bupropion Hydrochloride Sustained-Release or placebo treatment groups in a 1:1 ratio using a computer-generated table of random numbers through the use of the Randomization.com program. Subjects will be randomized to Bupropion Hydrochloride Sustained-Release 150mg b.d. (n = 35) or placebo b.d (n = 35)

## **8.2 Blinding**

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments. Access to the randomization code will be strictly controlled. Besides, the packaging and labeling of test

and control treatments will be identical to maintain the blind. The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management

### **8.3 Formulation of Test and Control Products**

#### **8.3.1 Description**

Bupropion hydrochloride sustained-release (Wellbutrin SR™) tablets are biconvex purple film-coated with a white core.

#### **8.3.2 Treatment Regimen**

##### **8.3.2.1 Route**

The drugs are taken orally

##### **8.3.2.2 Regime**

Bupropion hydrochloride sustained-release started at 150mg on morning (0800) from day 1 to day 3. Dose increased to 150mg on morning (0800) and evening (1800) from day 4 onwards. The dose can be reduced to 150mg/day if patients are not able to tolerate a higher dose. The treatment continues until day 42.

### **8.4 Preparation and Administration of Study Drug**

Study drug will be maintained and dispensed by the study coordinator. Tablets will be used as supplied, meaning that there is no further study drug preparation required. Study drug is administered orally.

### **8.5 Prior and Concomitant Therapy**

All prior and/or concomitant medical therapy will be documented

Anxiolytic drugs (clonazepam, lorazepam, valium and alprazolam) and methadone are permitted for agitation, anxiousness or insomnia.

All other medication which can improve the sexual function except the study drugs are not permitted during the study.

### **8.6 Packaging and Labeling**

The study drug will be repacked in the standard capsules by the research assistant who is not involved in the assessment of the study. The study drug and placebo will be packaged in sets of 11 (1 tablet per day for 3 days, followed by 2 tablets per day for 4 days.) for the first week. Subsequently, the study drug and placebo will be packaged in sets of 14 (2 tablets per day for 7 days.). Each packet (kit) of study drug will be labeled with the required FDA warning statement, the protocol number, a treatment number, and directions for patient use and storage.

## **8.7 Receiving, Storage, Dispensing and Return**

### **8.7.1 Receipt of Drug Supplies**

Upon receipt of the of the study drugs, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (study drug or comparator) will be documented in the study files. The investigator will notify the Company of any damaged or unusable study treatments that were supplied to the investigator's site.

### **8.7.2 Storage**

Stock study drug and drug packaged in patient kits within the research centre and study drug that has been dispensed to the Investigator, will be stored in a locked cabinets with climate control maintaining the temperatures within a range of 20°-25° C. Access to study drug within the research centre will be controlled by the staff, and access to study drug dispensed to the Investigator will be controlled by the Investigator and the Investigator's study staff.

### **8.7.3 Dispensing of Study Drug**

All study drugs will be dispensed by investigator or their designated study staff.

### **8.7.4 Return or Destruction of Study Drug**

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study. . Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. After appropriate accounting, unused study drug will be destroyed on site with the date of this action documented in the study files.

## **8.8 Measures of Treatment Compliance**

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers. The research coordinator will conduct pill counts at each visit of all study subjects. Unused amounts will be documented. Proper drug dosing will be reviewed with subjects at each visit with clear instructions to take all study drugs as directed.

## **9 STUDY PROCEDURES AND GUIDELINES**

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject

## **9.1 Clinical Assessments**

### **9.1.1 Concomitant Medications**

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Study Days and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

### **9.1.2 Demographics**

Demographic information (date of birth, gender, race) will be recorded at Screening.

### **9.1.3 Medical History**

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

### **9.1.4 Physical Examination**

A complete physical examination will be performed by the investigator at Screening. Vital Signs, Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at Baseline/Screening and at Study Days.

### **9.1.5 Adverse Events**

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

## **9.2 Clinical Laboratory Measurements**

### **9.2.1 Blood investigation**

Approximately 20 ml (4 teaspoons) of blood will be collected at visit 0 (baseline) for a complete blood count (hemoglobin, white blood cell count, white blood cell differential, and platelet count), blood count, serum sodium, potassium, chloride, bicarbonate, creatinine, fasting glucose, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), total testosterone (TT), free testosterone (FT), estradiol (E2), luteinizing hormone (LH), prolactin, Hepatitis B, C and HIV. Approximately 5ml(1 teaspoon) of blood will be collected during visit 3 and 6 for liver function test: aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT).

### **9.2.2 Urinalysis**

Urine will be obtained and tested for amphetamine, methamphetamine, marijuana and opioid in their urine by using F.A.C.T.S combo drug testing. The F.A.C.T.S combo drug testing is a competitive immunoassay utilizing highly specific reactions between antibodies and antigens for the detection of drugs which may be presented in the urine

specimens. During the testing, the urine specimen migrates upward by capillary action. If a drug is present in the urine specimen above the cut-off concentration, it will saturate all the binding sites of the antibody, and the colored line will not form in the test line region. To serve as a procedural control, a colored line will appear at the control line region. Hence, positive test will only have one line and negative test will have two lines on the test strip.

## **10 EVALUATIONS BY VISIT (REFER APPENDIX 1.)**

### **10.1 Visit 0(Screening visit and Randomization)**

Review the study with the subject and obtain written informed consent. Those who are willing to participate and consented will be screened for eligibility. A complete physical examination will be performed and blood will be collected for clinical laboratory tests. Urine will be collected for testing amphetamine, methamphetamine, marijuana and opioid. A Mini International Neuropsychiatric Inventory (MINI) will be administered to obtain DSM-IV diagnoses of opioid dependence and rule out other psychiatric disorders. MADRS, Malay version, OTI, WHOQoL-Brief, Malay version, Mal-GRIMS, CGI-SF, IIEF15, and ASEX will be completed. Eligible subjects will be scheduled for Visit 1 in 7 days.

### **10.2 Visit 1 (week 1)**

Eligible subjects will be randomized and started either the study drug or placebo. Concomitant medications will be reviewed; abbreviated physical examination will be performed, vital signs will be recorded, Urinalysis for illicit drug and electrocardiography will be recorded. Eligible subjects will be scheduled for Visit 2 in 7 days.

### **10.3 Visit 2 (week 2)**

Any Adverse Experiences will be recorded. Subject diary for adverse experiences and dosing compliance will be reviewed. Concomitant medications will be reviewed; abbreviated physical examination will be performed, vital signs will be recorded, CGI-SF, IIEF15, and ASEX will be completed. Eligible subjects will be scheduled for Visit 3 in 7 days.

### **10.4 Visit 3 (week 3)**

Any Adverse Experiences will be recorded. Subject diary for adverse experiences and dosing compliance will be reviewed. Concomitant medications will be reviewed; abbreviated physical examination will be performed, vital signs will be recorded, Urinalysis for illicit drug and electrocardiography will be recorded. Approximately 5ml(1 teaspoon) of blood will be collected for liver function test: AST(GOT) and ALT(GPT). CGI-SF, IIEF15, and ASEX will be completed. Eligible subjects will be scheduled for Visit 4 in 7 days.

### 10.5 Visit 4 (week 4)

Any Adverse Experiences will be recorded. Subject diary for adverse experiences and dosing compliance will be reviewed. Concomitant medications will be reviewed; abbreviated physical examination will be performed, vital signs will be recorded, CGI-SF, IIEF15, and ASEX will be completed. Eligible subjects will be scheduled for Visit 6 in 7 days.

### 10.6 Visit 5 (week 5)

Any Adverse Experiences will be recorded. Subject diary for adverse experiences and dosing compliance will be reviewed. Concomitant medications will be reviewed; abbreviated physical examination will be performed, vital signs will be recorded, CGI-SF, IIEF15, and ASEX will be completed. Eligible subjects will be scheduled for Visit 6 in 7 days.

### 10.7 Visit 6 (week 6) (end of study drug)

Any Adverse Experiences will be recorded. Subject diary for adverse experiences and dosing compliance will be reviewed. Concomitant medications will be reviewed; abbreviated physical examination will be performed, vital signs will be recorded, Urinalysis for illicit drug and electrocardiography will be recorded. Approximately 5ml(1 teaspoon) of blood will be collected for liver function test: AST(GOT) and ALT(GPT). CGI-SF, IIEF15, and ASEX will be completed. CGI-SF, IIEF15, and ASEX will be completed.

### 10.8 Early Withdrawal Visit

Any Adverse Experiences will be recorded. Subject diary for adverse experiences and dosing compliance will be reviewed. Concomitant medications will be reviewed; abbreviated physical examination will be performed, vital signs will be recorded, Urinalysis for illicit drug and electrocardiography will be recorded.

## 11 STATISTICAL PLAN

### 11.1 Sample Size Determination

For the hypothesis testing of this study, the significance level was set at 5%. The hypothesis involves comparison of 2 groups on the mean of a continuous outcome. Each group of 35 provides 90% power to detect an effect size of 0.5.

### 11.2 Statistical Methods

Data Screening and Cleaning: Principal investigator will perform the data analyses. Prior to performing analyses, standard data screening/cleaning procedures will be applied. These procedures will screen the data for data-entry errors, check for outliers, assess the extent and pattern of missing data, and check that appropriate assumptions of Normality are met whenever necessary. Because of the size of the sample, it is unlikely that the randomization will result in significant imbalance of the distributions of demographic or other variables across the treatment groups. However, the randomization will be checked by comparing the groups on relevant background variables. The comparisons will use

analyses of variance for continuous variables and log-linear models for discrete or ordinal responses. Variables on which the groups show significant differences may be included as covariates in later analyses.

Linear Mixed Model: The analyses described below will involve the use of linear mixed model. These models extend the traditional repeated-measures framework in several ways. The main advantage is that it allows flexible regression modeling of patterns over time. It deals easily with measurements at irregular time points and automatically deals with missing data. It also allows a variety of structures for residual variations and correlations. In the present setting, the main explanatory variables will be medication group and time. Additional terms and random effects are included for each individual to model the correlation between observations on the same individual. In terms of missing data, they require that the data be missing at random, which is often reasonable. This means that the linear mixed model effectively assume that the missing data are similar to the observed data that do not drop out. In all analyses, the assumptions underlying the application of all the statistical methods that are used will be examined, principally through the use of standardized residuals, influence diagnostics, and graphical displays.

Analyses of the Primary and Secondary Endpoints: The effect of Bupropion Hydrochloride Sustained-Release in improving the sexual dysfunction in the subjects is measured with CGI-SF at baseline, week 2, 4 and 6. The secondary outcomes are measured with IIEF15, its 5 domains and ASEX at baseline, week 2, 4 and 6. These repeated measurements will be analyzed using linear mixed-effects model. While these analyses are exploratory, they will provide useful information on differences in trends of reduction of depression and other outcomes between the Bupropion Hydrochloride Sustained-Release and placebo groups.

### 11.3 Subject Population(s) for Analysis

Efficacy analysis will be performed on ITT basis. Any subject randomized into the study, regardless of whether they received study drug will be included into the analyses.

### 11.4 Data Management

A computerized data entry and management system will be developed during the initial project months that will enter all study data. All data will be entered using data entry programs.

## 12 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

### 12.1 Adverse Events

**Definitions:** Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the protocol or consent form and the patient information sheets)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

### Adverse Event

An **adverse event (AE)** is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

### AE Severity

Table 1: below should be used to grade severity. It should be pointed out that the term “severe” is a measure of intensity and that a severe AE is not necessarily serious.

**Table 1. AE Severity Grading**

| Severity (Toxicity Grade) | Description   |
|---------------------------|---|
| Mild (1)                  | Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well. |
| Moderate (2)              | Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.   |
| Severe (3)                | Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.  |
| Life-threatening (4)      | The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.  |

### AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.



**Table 2. AE Relationship to Study Drug**

| <b>Relationship to Drug</b> | <b>Comment</b>  |
|-----------------------------|---|
| Definitely                  | Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.                         |
| Probably                    | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions. |
| Possibly                    | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.   |
| Unrelated                   | An event that can be determined with certainty to have no relationship to the study drug.   |

## 12.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

### Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 14 days following the last administration of study treatment.

**Preexisting Condition**

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

**General Physical Examination Findings**

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

**Post-study Adverse Event**

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the ethical committee of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

**Abnormal Laboratory Values**

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

**Hospitalization, Prolonged Hospitalization or Surgery**

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

### **Recording of Adverse Events**

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

### **Reporting of Serious Adverse Events and Unanticipated Problems**

The investigator and sub-investigators report all types of unanticipated problems, adverse events and serious adverse events to the ethical committee within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and send to the EC within 24 hours. The investigator will keep a copy of this SAE form on file at the study site.

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others  
(see definitions, section 12.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- |                              |  |
|------------------------------|--|
| • Protocol number            | • Current status   |
| • Subject number             | • Whether study treatment was discontinued   |
| • A description of the event | • The reason why the event is classified as serious                                |
| • Date of onset              | • Investigator assessment of the association between the event and study treatment |

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will

assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the MEC, UMMC.

### **Unblinding Procedures**

While the safety of the subject always comes first, it is important to consider if unblinding the study therapy is necessary to ensure a subject's safety. If the SAE is confirmed due to the study therapy, the timeline of reporting is within 24 hours, however, in cases where unblinding was not associated with an SAE, the timeline of reporting is within 1 week.

### **Medical Monitoring**

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

### **Protection of Subjects**

Complementing the safety measures noted above, additional procedures will be followed to protect the safety of the research subjects. Potential Subjects will be screened for medical illnesses that would preclude the use of methylphenidate. Specifically, these include known allergies to this agent. Subjects selected for the study will be evaluated daily while receiving study drug treatments. AEs will be monitored daily and a study physician will be available at all times to evaluate and treat adverse effects of the medication. On a daily basis, vital signs will be obtained. Significant AEs will result in exclusion from the study (see Clinical Trial Discontinuation Criteria). Subjects will be given a 24-hour emergency number they can call if necessary. The investigator or sub-investigators will clinically follow all subjects who are discontinued due to serious AEs until the AE resolves and becomes completely stable, unless a referral to another physician (i.e. specialist) is clinically indicated or requested by the subject.

## **13 DISCONTINUATION AND REPLACEMENT OF SUBJECTS**

### **13.1 Early Discontinuation of Study Drug**

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment

- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

### **13.2 Withdrawal of Subjects from the Study**

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early, should have an early discontinuation visit. Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

## **14 PROTOCOL VIOLATIONS**

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- non-compliance with study drug regimen

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

## **15 DATA COLLECTION, RETENTION AND MONITORING**

### **15.1 Confidentiality**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Authorities

### **15.2 Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, X-rays, subject files, and records kept at the pharmacy and at the laboratories involved in the clinical trial.

### **15.3 Data Quality Control and Reporting**

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

### **15.4 Records Retention**

These medical notes and documents will be retained in the UMMC Medical Record Department.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study.

## **16 STUDY MONITORING, AUDITING, AND INSPECTING**

### **16.1 Study Monitoring Plan**

This study will be monitored according to the monitoring plan in Attachment \_\_\_\_\_. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

### **16.2 Auditing and Inspecting**

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance

groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

## **17 ETHICAL CONSIDERATIONS**

The study will be conducted according to the Declaration of Helsinki, Good Clinical Practice (International Conference on Harmonization guidelines), MEC, UMMC, NMRR research policies and procedures

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet

### **17.1 Informed Consent Form**

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment \_\_\_\_ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB/EC for the study. The formal consent of a subject, using the IRB/ED-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

The investigator or sub-investigators will obtain informed consent before any study procedures occur, explaining all procedures in detail in an individual session. The consent form and explanation will include; detailed information about methylphenidate, the rationale for why it is being studied, frequency of dosing, and length of treatment, potential side effects and risks, safeguards and emergency procedures. Information will also be provided about the psychosocial treatment, including the frequency and length of visits. The number and frequency of the research interviews and self-assessments will be described in details. Subjects will be assured that their participation is voluntary and that withdrawal from the study would not jeopardize current or future treatment. All subjects will be informed of potential risks and benefits involved in the study, including side effects of methylphenidate. Randomization will be explained to the subjects.

## **18 STUDY FINANCES**

### **18.1 Funding Source**

Will apply for university grant

## **18.2 Conflict of Interest**

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by MEC, UMMC.

## **19 PUBLICATION PLAN**

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided for the purposes of performing the study, will be published or passed on to any third party without the consent of the principle investigator. The principal Investigator will be responsible for publishing the primary results of this study. All subsequent publications will be at the discretion of the Principal Investigator



## APPENDIX 1:

|  | Screening test | During treatment with the study drug |        |        |        |        |        |                  |
|--|----------------|--------------------------------------|--------|--------|--------|--------|--------|------------------|
| Time   | baseline       | 1 week                               | 2 week | 3 week | 4 week | 5 week | 6 week | At withdrawal    |
| Visit  | Visit 0        | Visit1                               | Visit2 | Visit3 | Visit4 | Visit5 | Visit6 |                  |
| Informed consent   | √              |                                      |        |        |        |        |        |                  |
| Prescription of study drug                                   |                | √                                    | √      | √      | √      | √      | √      |                  |
| Treatment compliance   |                | √                                    | √      | √      | √      | √      | √      | √                |
| Interview for assessment of sexual dysfunction(1)            | √              |                                      | √      |        | √      |        | √      | √                |
| New symptoms that occur during treatment with the study drug |                | √                                    | √      | √      | √      | √      | √      | √(until 14 days) |
| Body weight  |                | √                                    | √      | √      | √      | √      | √      | √                |
| Blood pressure/pulse rate/body temperature                   |                | √                                    | √      | √      | √      | √      | √      | √                |
| Blood test (2)   | 20ml           |                                      |        | 5ml    |        |        | 5ml    |                  |
| Urinalysis(3)  | √              | √                                    |        | √      |        |        | √      |                  |
| Electrocardiography  | √              | √                                    |        | √      |        |        | √      |                  |

- (1) At baseline: Montgomery-Åsberg Depression Rating Scale (MADRS, Malay version ), Mini International Neuropsychiatric Interview (M.I.N.I), Opiate Treatment Index (OTI) and World health organization Quality of Life-Brief Scale (WHOQoL-Brief, Malay version, Malay Version of the Golombok-Rust Inventory of Marital State (Mal-GRIMS), International Index of Erectile Function (IIEF), Clinical Global Impression Scale adapted for Sexual Function (CGI-SF), Arizona Sexual Experience Scale (ASEX). Then, IIEF, CGI-SF, ASEX at week 2, 4, and 6.
- (2) Blood test: Approximately 20 ml (4 teaspoons) of blood will be collected at visit 0 (baseline) for Full blood count, Renal function test, Liver function test, Fasting blood sugar, total testosterone (TT), free testosterone (FT), estradiol (E2), luteinizing hormone (LH), and prolactin. Hepatitis B, C and HIV. Approximately 5ml(1 teaspoon) of blood will be collected during visit 3 and 6 for liver function test: AST(GOT) and ALT(GPT).
- (3) Urinalysis for illicit drug

## 20 REFERENCES:

1. Laumann, E.O., A. Paik, and R.C. Rosen, *Sexual dysfunction in the United States*. JAMA: the journal of the American Medical Association, 1999. **281**(6): p. 537-544.
2. Macdonald, S., et al., *Nithsdale Schizophrenia Surveys 24: sexual dysfunction Case—control study*. The British Journal of Psychiatry, 2003. **182**(1): p. 50-56.
3. Rosen, R.C., *Prevalence and risk factors of sexual dysfunction in men and women*. Curr Psychiatry Rep, 2000. **2**(3): p. 189-95.
4. Grube, M. and H. Weigand-Tomiuk, *Sexual dysfunctions in a group of psychiatric in-patients*. Psychiatrische Praxis, 2002. **29**(4): p. 194.
5. Oksuz, E. and S. Malhan, *The prevalence of male sexual dysfunction and potential risk factors in Turkish men: a Web-based survey*. International journal of impotence research, 2005. **17**(6): p. 539-545.
6. Mattick, R.P., et al., *Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence*. Cochrane Database Syst Rev, 2009. **3**.
7. Yee, A., H.S. Loh, and C.G. Ng, *The Prevalence of Sexual Dysfunction among Male Patients on Methadone and Buprenorphine Treatments: A Meta-Analysis Study*. The Journal of Sexual Medicine, 2014. **11**(1): p. 22-32.
8. Brown, R., et al., *Methadone maintenance and male sexual dysfunction*. Journal of addictive diseases, 2005. **24**(2): p. 91-106.
9. Hallinan, R., et al., *Erectile dysfunction in men receiving methadone and buprenorphine maintenance treatment*. The Journal of Sexual Medicine, 2008. **5**(3): p. 684-692.
10. La Pera, G., et al., *Sexual dysfunction prior to first drug use among former drug addicts and its possible causal meaning on drug addiction: preliminary results*. The journal of sexual medicine, 2008. **5**(1): p. 164.
11. Maremmani, I., *The Principle and Practice of Methadone Treatment*. 2010: Europad.
12. Balon, R. and R.T. Segraves, *Handbook of sexual dysfunction*. 2005: CRC Press.
13. Yee, A., et al., *Clinical factors associated with sexual dysfunction among men in methadone maintenance treatment and buprenorphine maintenance treatment: a meta-analysis study*. International journal of impotence research, 2014.
14. Trajanovska<sup>1</sup>, A.S., et al., *Sexual dysfunction as a side effect of hyperprolactinemia in methadone maintenance therapy*. Med Arh, 2013. **67**(1): p. 48-50.
15. Van Ree, J.M., et al., *Endogenous opioids and reward*. European journal of pharmacology, 2000. **405**(1): p. 89-101.
16. Dominguez, J.M. and E.M. Hull, *Dopamine, the medial preoptic area, and male sexual behavior*. Physiology & behavior, 2005. **86**(3): p. 356-368.
17. Gradin, V.B., et al., *Abnormal Brain Activity During a Reward and Loss Task in Opiate-Dependent Patients Receiving Methadone Maintenance Therapy*. Neuropsychopharmacology, 2013.

18. Argiolas, A. and M.R. Melis, *Neuropeptides and central control of sexual behaviour from the past to the present: A review*. Progress in neurobiology, 2013. **108**: p. 80-107.
19. Tatari, F., et al., *Bupropion in Methadone Induced Erectile Dysfunction*. Life Science Journal, 2013. **10**(9s).
20. <https://www.gsksource.com/gskprm/htdocs/documents/WELLBUTRIN-SR-PI-MG.PDF>.

## 21 ATTACHMENTS

- Sample Consent Form
- Study Procedures Flowchart/Table
- Patient information sheets
- Medical Monitoring Plan
- Descriptions of measuring scales
- Laboratory tests normal cutoff values