

CLINICAL STUDY PROTOCOL

A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

Randomized study Evaluating the efficacy and SafeTy of a ONce nightly formulation of sodium oxybate (REST-ON Study)

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EudraCT Number: 2016-000359-29

IND Number: 126321


INC Research Study Number: 1006624

Investigational Product: Sodium Oxybate for Extended-Release Oral Suspension (FT218)

Phase: 3

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Flamel Ireland Limited, a wholly owned subsidiary of
Flamel Technologies

Contract Research Organization: 

Protocol Date: 01 August 2019

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1 PROTOCOL APPROVAL SIGNATURES


Protocol Title: A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

Protocol Number: CLFT218-1501

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatories

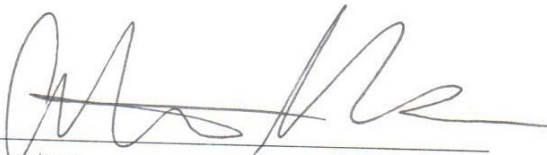
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2 STUDY PERSONNEL

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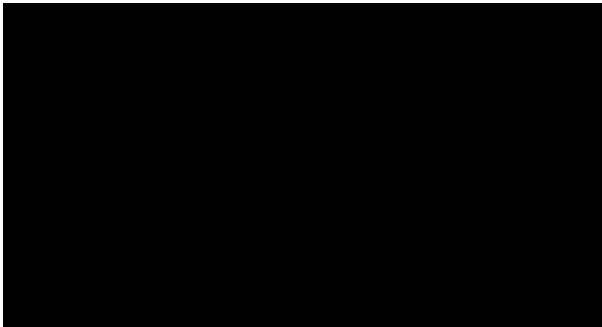
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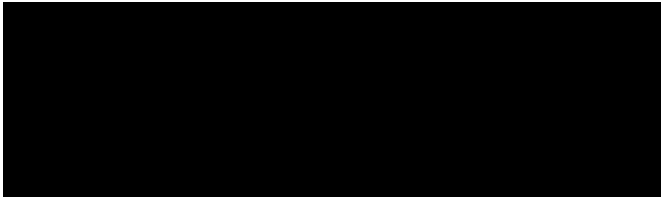
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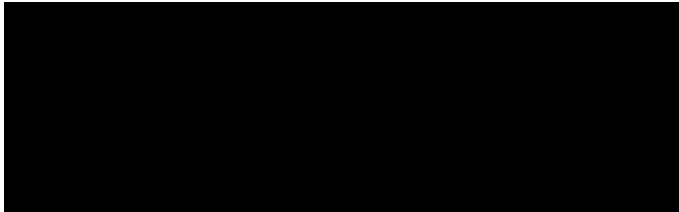
Central Clinical Laboratory



Interactive Response Technology (IRT)



Central Scoring Laboratory



3 SYNOPSIS

Protocol Number:

CLFT218-1501

Title:

A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

Investigational Product:

Sodium oxybate for extended-release oral suspension (FT218)

Study Centers:

Approximately 60 centers across the United States, Canada, and Europe

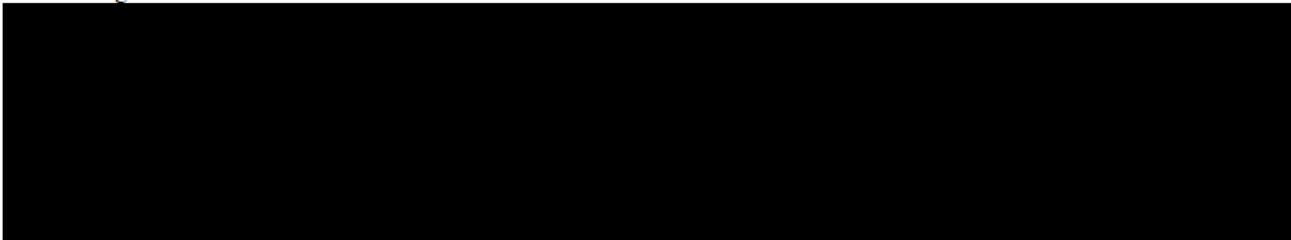
Phase:

Phase 3

Objectives:

Primary objective: To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating excessive daytime sleepiness (EDS) in both type 1 narcolepsy (NT1) and type 2 narcolepsy (NT2) subjects as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT) and by the Clinical Global Impression (CGI) rating of sleepiness, and to compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating cataplexy in NT1 subjects as measured by the number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary.

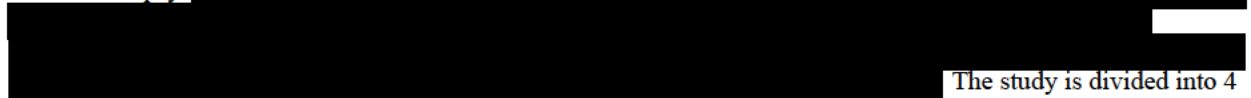
Secondary/exploratory objectives: To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo for the following outcomes:



Safety objective: To evaluate the relative safety of FT218 compared to placebo.

Study Design:

This is a double-blind, randomized, placebo-controlled, 2-arm multicenter clinical study to assess the efficacy and safety of a once nightly formulation of sodium oxybate (FT218) for the treatment of EDS and cataplexy in subjects with narcolepsy.



The study is divided into 4 sequential study periods. The study design incorporates scheduled dose titration to stabilized dose administration of FT218.

Two populations of narcoleptic subjects will be studied in a single parallel group design: 1) narcolepsy with both EDS and cataplexy (NT1), and 2) narcolepsy with EDS but with no cataplexy (NT2).

The study treatment period from screening to follow-up will last approximately 17 weeks. There is a 3-week screening period, followed by a central assessment of PSG and next-day MWT screening results (may take up to 2 days). If the subject is eligible, then randomization occurs. After randomization, dosing must start within 6 days (the window from randomization to dosing is to allow delivery of study drug to the site, total time from PSG and MWT

to dosing will be no more than 7 days). For subjects randomized to the active arm of the study the maximum duration of treatment with FT218 will be 13 weeks incorporating up-titration over a period of 8 weeks with 5 weeks on stable dosing at 9.0 g/night. For subjects randomized to placebo, there is no exposure to the study treatment.

A follow-up visit will occur at least 1 week after the last dose of FT218 or placebo (i.e. Period 4, Visit 9, Week 15, Day 1 [+4/-0 (i.e. a minimum of 7 days after the last on study dose)]). Additional follow-up for safety surveillance and management will be done for unresolved adverse events (AEs) as determined by the study investigator.

Number of Subjects:**Treatment:**

FT218 or placebo dosing will follow a 4 period up-titration as follows: FT218 4.5 g or placebo daily for 1 week, FT218 6.0 g or placebo daily for 2 weeks, FT218 7.5 g or placebo daily for 5 weeks, and FT218 9.0 g or placebo daily for 5 weeks. Study drug will be taken orally at bedtime.

Study Duration:

There will be a 3-week screening period, a 13-week treatment period and a 1-week follow-up period. Total duration of the study will be approximately 17 weeks.

Study Population:

Male or female subjects 16 years of age or older; documented evidence of a diagnosis of NT1 or NT2 as, in part, determined by an overnight PSG and next-day multiple sleep latency test (MSLT) with 2 or more sleep-onset rapid eye movement (REM) periods with mean sleep latency in the pathological range *i.e.* < 8 minutes (screening, Visit 1) and MWT < 11 minutes (after 3-week screening period); current continuing presence of EDS as defined by subject report for the last 3 months and an ESS > 10; for NT1 only, current continuing presence of cataplexy as defined by subject report for the last 3 months; subjects may use concomitant stimulants, but must comply with the following: they must be on a stable dose of stimulants for at least 3 weeks prior to starting the screening process for this study; AND they must use the same stimulant regimen throughout the entire study period, including during screening and posttreatment periods.

Primary Endpoints:

The primary criteria that efficacy determination will be based on include:

- Longer MWT sleep latency
- Improvement in CGI sleepiness scores
- Fewer cataplexy attacks as recorded by Sleep and Symptom Daily Diary

Secondary/Exploratory Endpoints:**Efficacy:**

Efficacy assessments include MWT, CGI, Sleep and Symptom Daily Diary, nocturnal PSG, and ESS

Safety:

Safety assessments include AEs, laboratory parameters, vital signs, physical examination, 12-lead electrocardiogram, Columbia-Suicide Severity Rating Scale

Statistical Analysis:

A mixed-effects means model with repeated measures (MMRM) will be used to analyze change from baseline for each of the coprimary endpoints. Each model will include treatment, time, treatment-by time interaction, site and baseline score as fixed effects and subjects as random effects. [REDACTED]

The primary hypothesis tests of the efficacy of individual doses will be performed as contrasts within the mixed models. The hypothesis testing will proceed in the following order: first, to test hypotheses for EDS, both MWT and CGI will be examined for statistical significance for the 9.0 g dose using the data collected during Periods 3c(i), and 3c(ii). If both tests are significant, NCA for the same dose will be tested. If the first test fails (either MWT or CGI not significant), the data for the 9.0 g dose was not able to reject the null hypothesis of equality to placebo for either symptom. If the first test is significant (both MWT and CGI significant) but the second test (NCA) fails, the dose has been demonstrated to exceed placebo for EDS treatment but not for cataplexy. If both tests are statistically significant, the dose has been shown to be effective for EDS and cataplexy.

If the 9.0 g dose demonstrates efficacy for both EDS and cataplexy, the same sequence of testing will be followed for the 7.5 g dose using the data collected during Periods 3b(i) and 3b(ii). If the 7.5 g dose demonstrates efficacy for both EDS and cataplexy, the same sequence of testing will be followed for the 6 g dose using the data collected during Period 3a.

Each dose will be tested in a hierarchical order starting at the 9.0 g dose level at the 2-sided α level of 0.05. Efficacy tests for MWT and for CGI within a dose need not be adjusted, since both are required for demonstrating efficacy for EDS at that dose. Efficacy tests for NCA within a dose for demonstrating efficacy for cataplexy also need not be adjusted because the test is reached via a step down procedure. Within each step, rejection terminates all subsequent hypothesis tests, which will be deemed to be nonsignificant. A strictly exploratory analysis examining secondary/exploratory endpoints is also proposed to provide evidence of consistency. The type I error rate for these endpoints will all be tested at the α level of 0.05.

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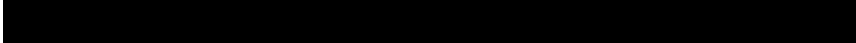

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5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

LIST OF ABBREVIATIONS

AE	adverse event
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CGI	clinical global impression
CNS	central nervous system
C _{max}	maximum concentration
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DNS	disturbed nocturnal sleep
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDS	excessive daytime sleepiness
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
FDA	United States Food and Drug Administration
FT218	sodium oxybate for extended-release oral suspension
GABA	gamma-aminobutyric acid
cGCP	current Good Clinical Practice
GHB	gamma-hydroxybutyric acid (sodium oxybate)
GI	gastrointestinal
HBs Ag	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HH	hypnagogic hallucinations
HLA	human leukocytes antigen
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
n	number of subjects with an observation
N	number of subjects in the dataset or population
NCA	number of cataplexy attacks
NT1	type 1 narcolepsy
NT2	type 2 narcolepsy
PI	principal investigator
PK	pharmacokinetic
PP	per protocol
PSG	polysomnography
REM	rapid eye movement
SAE	serious adverse event
SOC	system organ class

SOREM	Sleep-onset REM
SNRI	serotonin and norepinephrine re-uptake inhibitors
SP	sleep paralysis
SSRI	selective serotonin re-uptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TCA	tricyclic antidepressants
T_{max}	time to maximum concentration
US	United States
VAS	visual analog scale
WHO	World Health Organization

6 INTRODUCTION

6.1 Scientific Background

6.1.1 Summary

Sodium oxybate, also known as gamma-hydroxybutyric acid (GHB), was discovered in 1960. Sodium oxybate (GHB) is a metabolite of γ -aminobutyric acid (GABA) which is synthesized by neurons in the brain and functions as a neurotransmitter. Sodium oxybate is a central nervous system (CNS) depressant and produces dose-dependent sedation and anesthesia in laboratory animals. Sodium oxybate is currently indicated for the treatment of cataplexy and excessive daytime sleepiness (EDS) in subjects with narcolepsy at doses up to 9.0 g/night. In 2002, the US Food and Drug Administration (FDA) approved Xyrem[®] (sodium oxybate) oral solution as an orphan drug for the treatment of cataplexy in adult subjects with narcolepsy. In 2005, this approval was extended to the treatment of EDS for adults with narcolepsy. In Europe, sodium oxybate was granted Orphan Drug Designation in February 2003 (however, the orphan designation request has since been withdrawn), and the European Commission issued a decision in 2005 for its marketing authorization for the treatment of cataplexy in adult subjects with narcolepsy that was extended in 2007 to treating EDS in adults with narcolepsy.

As part of a recent meeting for the narcolepsy community initiated by the Food and Drug Administration (FDA), the FDA inquired “Assuming there is no complete cure for your condition, what specific things would you look for in an ideal therapy for your condition?” In an interim report circulated from the patient advocacy community, Unite Narcolepsy, summarizing the results from a patient survey with 1350 responses in preparation for the FDA meeting, the first statement responding to the FDA’s question was an excerpt from a patient response stating “A drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require 1 dose taken at bedtime resulting in 8 hours of restorative sleep”.¹

Flamel Technologies has developed a drug delivery technology designed to extend and/or delay the absorption of a drug in order to control its pharmacokinetic (PK) profile. Based on this proprietary controlled-release delivery technology, Micropump[®], Flamel Technologies has developed a new formulation of sodium oxybate which is more convenient for the subject in that it is dosed only once (i.e. at bedtime). The once nightly dosing is an improvement beyond the current approved dosing regimen for Xyrem that requires narcolepsy subjects to wake up in the middle of the night to take a second dose.

6.1.2 Disease Under Treatment

Narcolepsy is a chronic, life-disrupting neurologically-based sleep disorder characterized by 5 major symptoms, EDS, cataplexy, hypnagogic hallucinations (HH), sleep paralysis (SP), and disturbed nocturnal sleep (DNS). Narcolepsy is associated with increased morbidity,^{2,3} increased mortality,⁴ and reduced quality of life.⁵ In addition, there are significant social^{6,7} and economic^{8,9} impacts for subjects with narcolepsy, their families, and the healthcare system.¹⁰

Narcolepsy is currently dichotomized by the International Classification of Sleep Disorders-3 as either type 1 narcolepsy (NT1) or type 2 narcolepsy (NT2).¹¹ Type 1 narcolepsy is diagnosed by

the presence of EDS, cataplexy, a Multiple Sleep Latency Test (MSLT) indicating 2 or more sleep-onset rapid eye movement (REM) periods (SOREMs) and a mean sleep latency in the pathological range (i.e. < 8 minutes), and/or low hypocretin (≤ 110 pg/mL). Type 2 narcolepsy is diagnosed in the absence of cataplexy and when hypocretin levels are greater than 110 pg/mL, but the other diagnostic criteria for NT1 are met, including EDS, a MSLT indicating 2 or more SOREMs and a mean sleep latency in the pathological range (i.e. < 8 minutes), as well as the absence of another sleep disorder that better explains the EDS.

Narcolepsy is a rare disease, with 65,000 of the approximately 100,000 to 200,000 cases currently diagnosed in the US. Type 1 narcolepsy or narcolepsy with cataplexy is estimated to have a prevalence of 25 to 50 per 100,000 people and an incidence of 0.74 per 100,000 person-years internationally.^{12,13,14} Evidence indicates that NT1 is caused by the loss of hypocretin (also called orexin) cells in the hypothalamus. Thus, the best biological marker for NT1 is the reduction or complete deficiency of hypocretin in the cerebrospinal fluid.

Over 92% of Caucasian subjects with NT1 carry the human leukocytes antigen (HLA)-DQB1*06:02, while HLA-DQB1*06:03 allele confers a strong protection.^{15,16} The association with specific HLA alleles has allowed for the hypothesis that narcolepsy is an autoimmune disease, and progress has been made further substantiating an autoimmune origin for NT1 including: 1) anti-TRIBBLES-2 antibodies¹⁷, 2) elevated antistreptolysin O titers discovered close to disease onset¹⁸, and 3) the association with a polymorphism of T-cell receptor alpha gene and a polymorphism of the purinergic receptor P2RY11 gene.¹⁹ However, the mechanism for this autoimmune process remains unknown.

6.1.2.1 Symptoms of Narcolepsy

The hallmark symptom of narcolepsy is EDS, and is hence required for the diagnosis of narcolepsy. It is also the most troublesome symptom and the one for which subjects most commonly seek treatment. Excessive daytime sleepiness is defined as the inability to stay awake and alert during the day, resulting in periods of involuntary sleep episodes or unintended lapses into “drowsiness” during activities of daily living. In narcolepsy, EDS can exist despite adequate nighttime sleep, is not caused by another disease or condition which better explains the EDS, or persists when other conditions known to also cause EDS are treated. The chronic and severe nature of EDS predisposes these subjects to deficits in multiple areas of functioning. When alertness is compromised (i.e. sleepiness is pervasive), performance may be diminished across a variety of cognitive functions, work related safety may be compromised, and productivity and overall quality of life may suffer. It is possible the performance deficits may precipitate reduced patient-reported quality of life and difficulty with achievement in work and/or school. Beyond this, the sleepiness can be so omnipresent as to cause subjects to socially withdraw, making relationships with family and friends difficult to maintain and potentially strained.

Cataplexy, in the presence of EDS, is suggestive of NT1 and an indication for objective testing to confirm the diagnosis. Cataplexy is defined as a sudden muscle weakness episode and can affect a few muscles (for example, facial muscles) or all skeletal muscles at once. As a result of the muscle weakness, subjects momentarily have head nodding from weakness in the neck muscles, sagging of the jaw, buckling of the knees, dropping of objects from hands, and/or dysarthria or

inability to speak during the episode. Sometimes they may slump or fall forward onto the ground, either all at once or more gradually.

Cataplexy attacks are typically brief, on average, lasting from milliseconds to 1 to 2 minutes. Cataplexy is typically triggered by emotions, most often by telling or hearing a joke, laughing, or becoming angry. These emotions have been combined to successfully identify cataplexy among cases and lack of cataplexy among controls with remarkable specificity. For those with cataplexy, though, a wide range of emotions may be triggers, including surprise, rage, fear, enjoyment, love, accomplishment, and/or satisfaction from accomplishment (e.g. winning in an athletic competition). Sometimes the emotions cause cataplexy in situations with a social component, meaning that others are involved in eliciting the emotion, including other family members, friends, children, and/or pets. At initial presentation and close to symptom onset, and especially in children and teenagers, the onset of a cataplexy attack may not be precipitated by an emotional trigger and can happen almost spontaneously, termed atypical cataplexy.

Cataplexy is the most narcolepsy specific symptom, and it is unclear as to how and why the frequency or severity varies across subjects and may or may not change over time. Cataplexy is hypothesized to be a manifestation of REM atonia in waking. Thus when these episodes last for longer periods of time they evolve into REM sleep episodes and are perceived by the subject as sleep episodes with no memory of the cataplexy which preceded them. The onset of cataplexy typically occurs after the onset of EDS. Less frequently it can occur years after the EDS. Aside from the emotional triggers for cataplexy attacks, withdrawal from REM suppressing drugs may also cause them.

Additional symptoms completing the narcolepsy pentad include HH (vivid dreams at sleep onset or offset that are more often associated with negative emotions), and SP (feeling unable to move the body during transition periods of sleep). These may occur simultaneously and are often frightening to the subject. More specific for narcolepsy is their occurrence at sleep onset. Like cataplexy, SP and HH are REM related phenomena. Thus, experiencing them at sleep onset is rare in the general population. Experiencing them at sleep offset may simply be an awakening from REM. Thus, their occurrence at sleep offset is seen in the general population.

Disturbed nocturnal sleep (DNS) is the second most common symptom among narcolepsy subjects.²⁰ The DNS observed in narcolepsy is distinct from that seen in insomnia. While subjects with insomnia have difficulty falling asleep at the beginning of the night and after nocturnal awakening, subjects with narcolepsy fall asleep faster than insomniacs and even the general population. Disturbed nocturnal sleep in narcolepsy is characterized by frequent brief awakenings or shifts to lighter stages of sleep during the sleep period that are transient, with increased Stage 1 sleep, and reduced deeper stages of sleep. Often this leaves subjects feeling poorly rested or that their sleep was not refreshing. The contribution of DNS to the EDS in narcolepsy is not well understood.

6.1.2.2 Pharmacologic Treatment Options

Treatments for narcolepsy aim to relieve its symptoms, and are not directed towards any target known to be in the pathophysiological pathway of the disease. Thus, treatment includes stimulants to relieve EDS, sodium oxybate for EDS and cataplexy, and REM suppressing drugs

including tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs), or monoamine oxidase inhibitors (MAOIs) to relieve cataplexy as well as HH and SP. The severity of the symptoms can vary greatly from one person to another, and thus the response to any given medication is similarly varied from subject to subject.

Stimulants improve EDS in narcolepsy (eg, modafinil, armodafinil, methylphenidate, dextroamphetamine, or methamphetamine).^{21,22} In diagnosed subjects, modafinil, armodafinil, and methylphenidate are often prescribed first to reduce EDS. Dextroamphetamine and methamphetamine are potential alternatives for subjects who do not respond satisfactorily to the “front line” stimulant options. Some subjects may need a combination of drugs or a mixture of short- and longer -acting medications for optimal treatment. This evidences the fact that while stimulants improve EDS they do not normalize it. This is confirmed by patient reports in systematic studies.^{23, 24}

Potent REM suppressing drugs (i.e. SSRIs, TCAs and MAOIs) are used to treat cataplexy as well as HH and SP; however, the efficacy of these drugs in treating cataplexy has not been established in controlled clinical studies, but is based on experience from off-label use. Sodium oxybate (GHB), was approved by the FDA as Xyrem in 2002 for the treatment of cataplexy in adults with NT1. Subsequently, the improvement in daytime sleepiness led to a label extension to treat EDS in both types of narcolepsy. Sodium oxybate is administered in 2 divided doses at night, taken at bedtime and approximately 2.5 to 4 hours later. Disturbed nocturnal sleep is a symptom of narcolepsy that does not currently have any drugs indicated for its treatment.

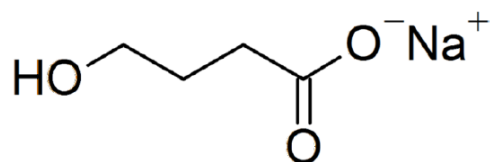
Despite the number of therapeutic options, narcolepsy medications are often not fully effective. It has been noted that there are drawbacks to the treatment regimen that can hinder compliance. Thus there remains a need for new agents. The twice nightly dosing regimen for Xyrem is inconvenient for subjects. With the availability of its drug delivery technology that allows for an extended release of drugs, Flamel Technologies has developed a new formulation of sodium oxybate, under investigation in this clinical study, with the objective to provide a therapy that is dosed only once at bedtime and provides subjects with the same level of efficacy and safety as the current twice nightly therapy.

6.2 Background to FT218 Controlled-Release Technology

6.2.1 Sodium Oxybate Drug Metabolism and Pharmacokinetics

The active ingredient of FT218, sodium oxybate, is a CNS depressant. Sodium oxybate is the nonproprietary name for the sodium salt of GHB, a metabolite of GABA, which is synthesized and accumulated by neurons in the brain. It is present at μM concentrations in all brain regions investigated as well as in several peripheral organs, particularly in the gastrointestinal (GI) system. Sodium oxybate is rapidly absorbed after oral administration with an absolute bioavailability of about 25% due to a large hepatic first pass effect. Pharmacokinetics are nonlinear, following oral administration, the plasma levels of sodium oxybate increase more than proportionally with increasing dose. The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible.

The efficacy and safety profiles of the currently marketed formulation of sodium oxybate, Xyrem, are well characterized. The molecular formula of FT218 active ingredient is $C_4H_7NaO_3$ with molecular weight of 126.1. The chemical name is sodium 4-hydroxybutanoate.



6.2.2 FT218 Development

Flamel has developed an extended-release oral suspension formulation of sodium oxybate, with the same active ingredient as the currently available and marketed product of sodium oxybate, Xyrem (NDA 021196) for treating EDS and cataplexy in subjects with narcolepsy. Flamel's formulation provides for an extended-release of the active ingredient by utilizing its proprietary technology, Micropump. This technology is the same as that used for the marketed drug product Coreg CR[®] (carvedilol, NDA 022012) for the treatment of hypertension, left ventricular dysfunction, and mild to severe heart failure. Coreg CR has been marketed in the US since 2007.

The Micropump technology is designed to extend and/or delay the absorption of drugs, which allows more controlled regulation of the drug's PK profile. FT218 is intended to provide a formulation of sodium oxybate which is dosed once at bedtime rather than the twice nightly dosing regimen of Xyrem which is taken at bedtime and then again 2.5 to 4 hours later. It is proposed that the FT218 once nightly dosing regimen represents an improved therapeutic option for subjects.

The FT218 drug product is composed of both immediate and modified release microparticles, where release is a function of time and pH. The formulation also contains a range of suspending agents and an acid buffer which impart both physical and chemical stability to the reconstituted aqueous suspension before administration. All FT218 formulation excipients are adequately qualified for use at the doses of the FT218 product.

6.3 Preclinical Experience and Animal Models

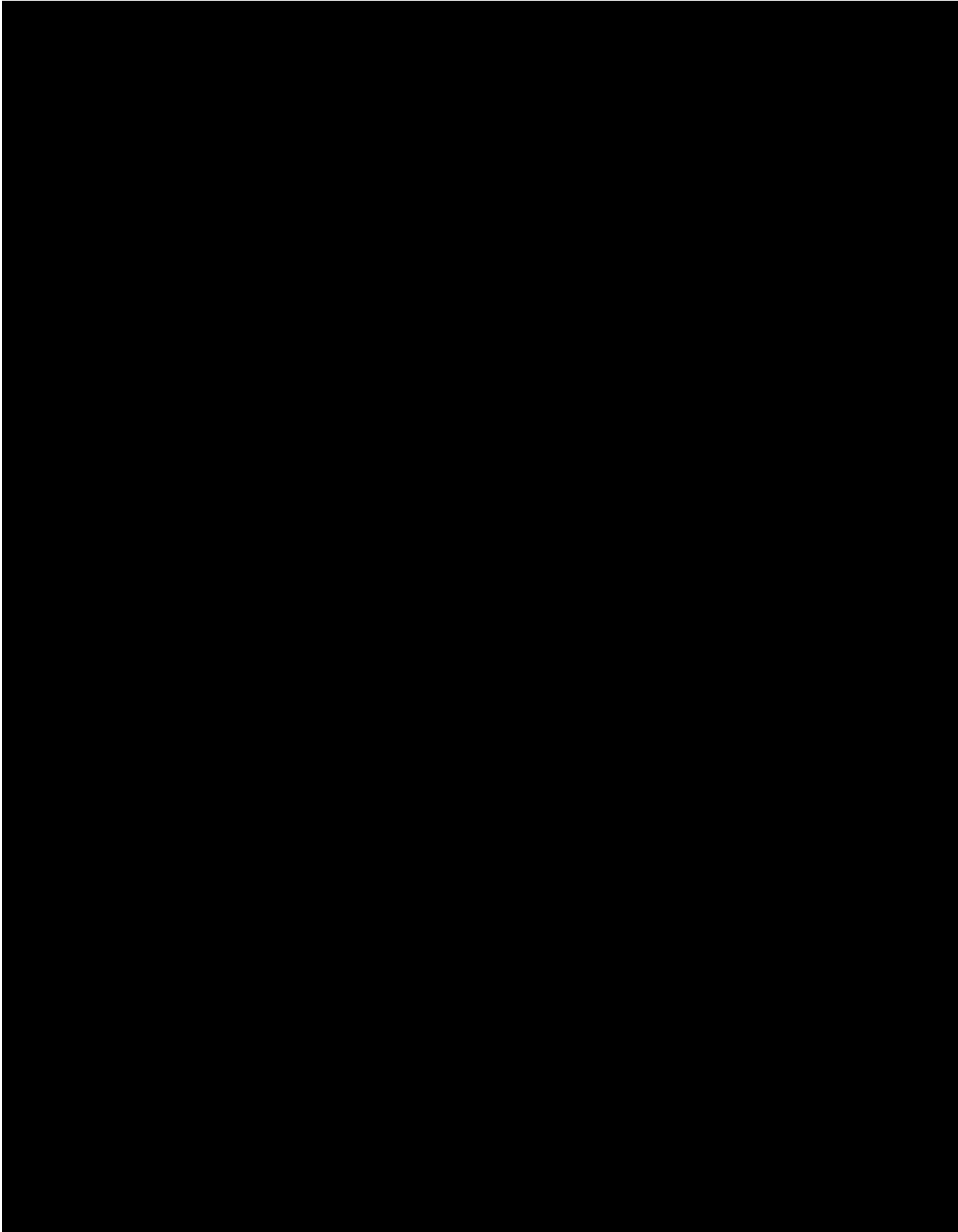
No nonclinical studies have been conducted during FT218 development. The reason was 2-fold, firstly, animal species are not relevant to evaluate the PK profile of FT218 due to the specific nature of the product's release mechanism and the differences between animal and human GI physiology. Secondly, the availability of nonclinical data on sodium oxybate, from the Xyrem nonclinical reviews by the FDA in 2002, the European Medicines Agency (EMA) in 2005, and by Health Canada in 2006 with later updates and assessment reports on intended extension of use.

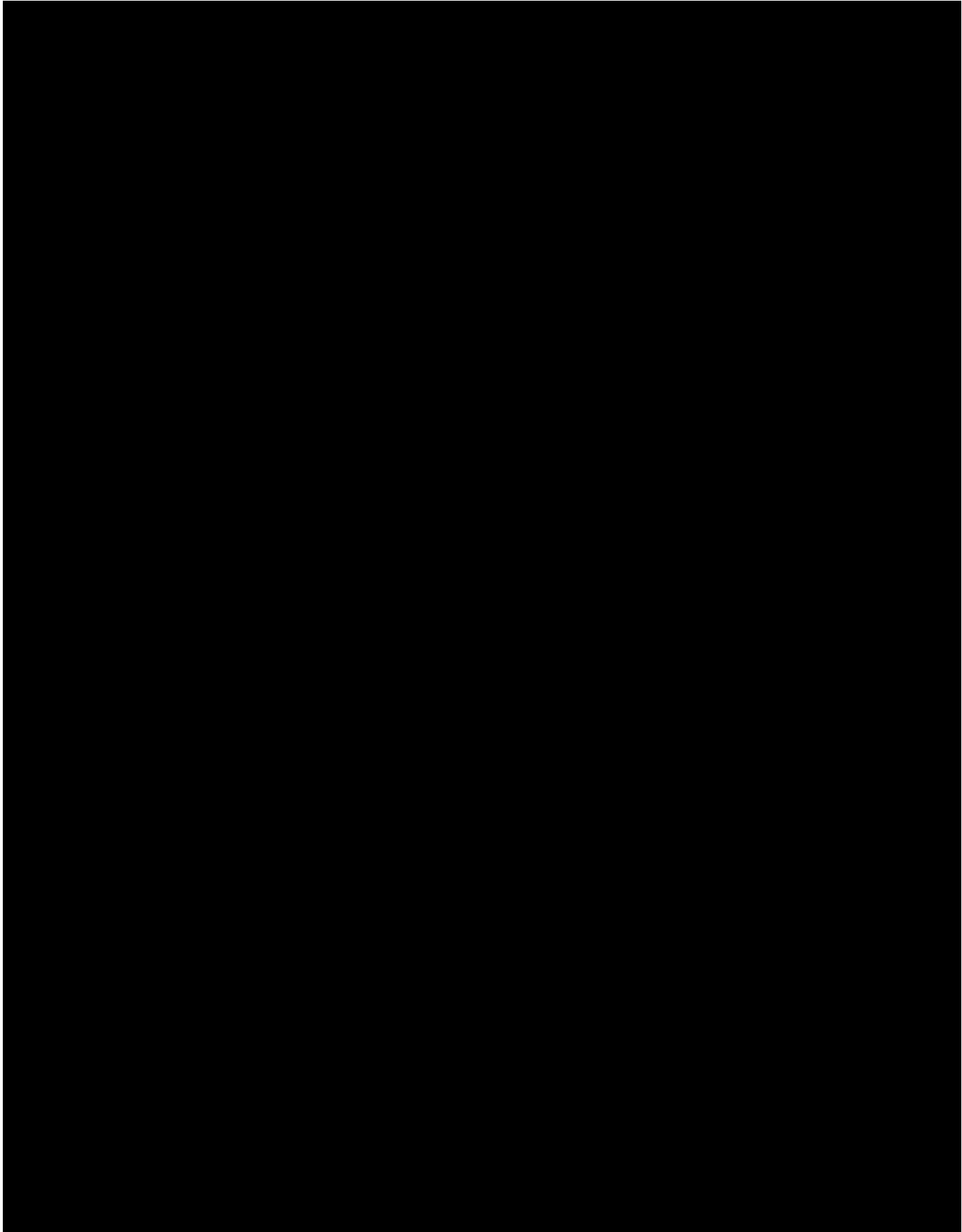
At pharmacological doses sodium oxybate acts as a CNS depressant. Sodium oxybate was found to have an affinity for 2 receptors in the brain, a GHB specific receptor and a GABA-B receptor. Sodium oxybate appears to have no affinity for the GABA-A receptor.

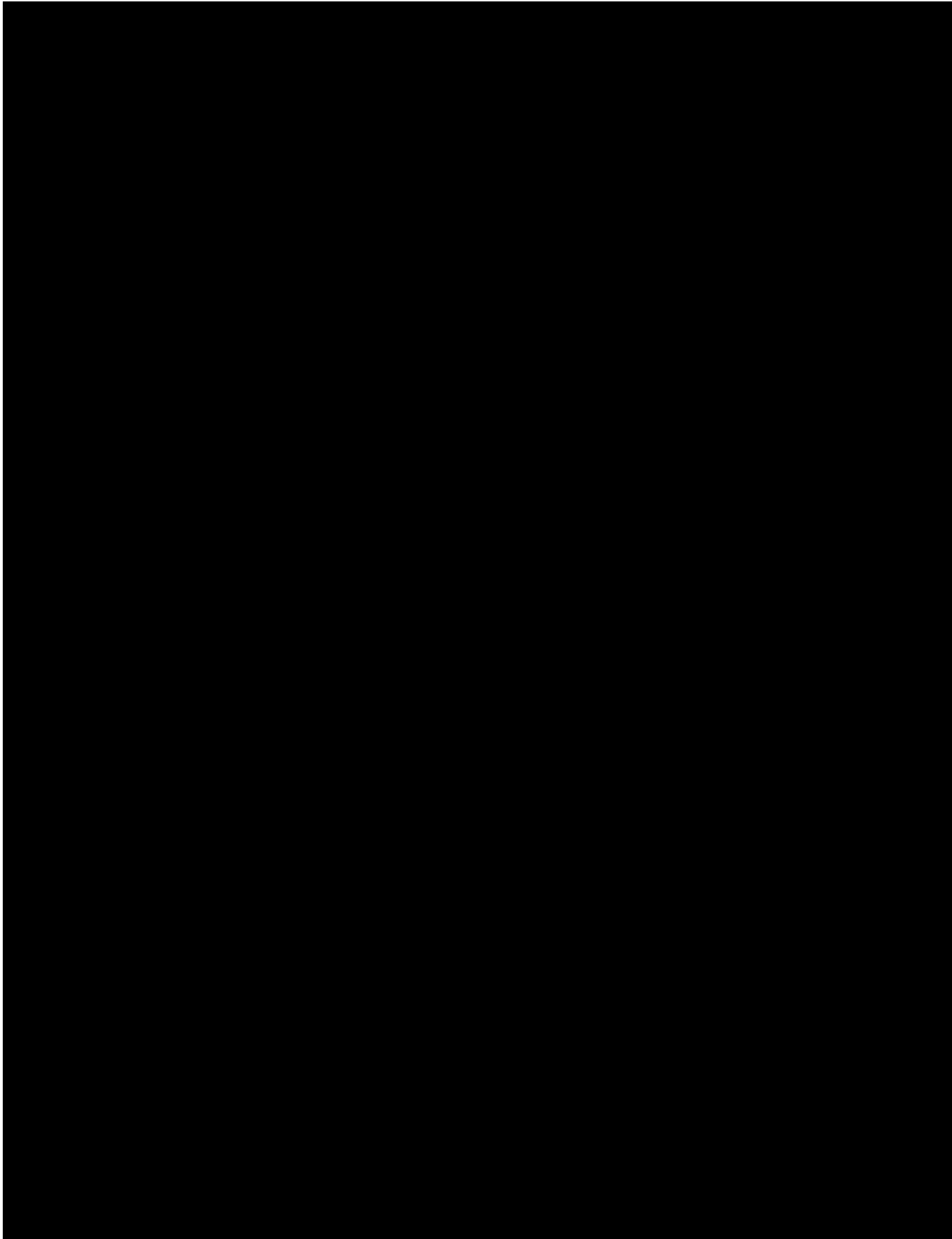
The submitted nonclinical data for Xyrem showed the safety of sodium oxybate in animal models, and it demonstrated transient drops in blood pressure (BP) as well as bradycardia. This was however limited to the species evaluated. Induced sleep from sodium oxybate, in both animal and man was found not to be accompanied by a decrease in oxygen consumption. The respiratory center remains sensitive to carbon dioxide although the slow-wave/delta sleep is enhanced. A slight drop in body temperature was observed in rats given sodium oxybate. Some animal studies report apparent epileptiform (epileptic/seizure-like) electroencephalography changes which have not been observed in human studies following sodium oxybate administration.

Pharmacodynamic interaction during the concomitant administration of sodium oxybate with CNS depressants such as benzodiazepines, barbiturates, and alcohol may result in additive increases in sedation and respiratory adverse effects. They are thus contraindicated.









6.5 Study Rationale

Sodium oxybate has shown significant efficacy for EDS and cataplexy in the treatment of NT1 and NT2. Flamel Technologies is proposing a new sodium oxybate drug product, FT218, which utilizes the company's proprietary Micropump technology. The proposed innovation is clinically relevant as the current marketed product, Xyrem, has to be taken twice during the night, 2.5 to 4 hours apart, which is a limitation.

The FT218 Phase 1 study (study PKFT218-1301) confirmed the expected PK properties of the FT218 formulation i.e. a release of the drug over at least 6 hours, a lower C_{max} and a residual plasma level at 8 hours after intake not significantly different than the reference. Overall, under the hypothesis of a PK exposure-clinical effect relationship, this study confirmed that FT218 will be as safe as the reference marketed product. The forced up-titration design of this study is expected to be particularly informative, allowing observations of efficacy and safety at 6.0, 7.5, and 9g doses. Three therapeutic doses will be tested under forced up-titration (6.0, 7.5, and 9.0 g) since no concentration/response relationship is known. The study allows for forced dose increments at fixed times from 4.5 g/night followed by 1.5 g/night increments until the final 9.0 g dose is reached. Subjects will remain on the 4.5 g dose for 1 week, the 6.0 g dose for 2 weeks, the 7.5 g dose for 5 weeks and the 9.0 g dose for 5 weeks. Evaluations for efficacy and safety for 6.0, 7.5, and 9.0 g will be done over a 12-week period (total of 13 weeks on study drug) relative to the placebo group.

The up-titration is based on the dosage schedule recognized as safe with Xyrem. A full efficacy assessment will occur for the 6.0 g/night dose after 3 weeks on study drug (including a titration from 4.5 g/night for the first week followed by 2 weeks at 6.0 g/night). The 7.5 g full efficacy

assessment will occur after 8 weeks on study drug (including 1 week at 4.5 g and 2 weeks at 6.0 g). A final titration occurs to maximum dose (i.e. 9.0 g). A full efficacy assessment will be done following 5 weeks on the final dose (that is following a total of 13 weeks on medication) relative to the placebo group. During both the 7.5 g and the 9.0 g 5-week treatment a partial efficacy assessment [REDACTED] will be carried out after 2 weeks on the respective doses.

The selected FT218 doses for the current study match the therapeutic dose range recognized as safe and effective for the reference drug product, Xyrem. All FT218 doses (6.0, 7.5, and 9.0 g) were selected for their safety and efficacy profile in treating subjects with narcolepsy based on previous studies with sodium oxybate. In addition, results from the Phase 1 PKFT218-1301 study indicated that the study formulation is safe at 4.5, 6.0, and 7.5 g/night in healthy volunteers. Given the PK characteristics of the current formulation of FT218, the proposed doses are not anticipated to be associated with any safety concerns.

Full safety and efficacy of FT218 will be evaluated in this clinical study. A double-blind, placebo-controlled randomized methodology has been identified as the optimal design to support efficacy and safety evaluation.

This FT218 clinical study has been designed to ensure conduct and analysis according to sound scientific principles to achieve study objectives. Placebo has been selected as the choice for the control group, as this will optimize inferences drawn from the study. It will provide for an undiluted evaluation of total pharmacological and treatment effect (i.e., study drug versus disease). In addition, this approach lends itself to a smaller sample size requirement.

Randomization will provide a means of assuring comparability of test groups in expectation and minimize selection bias, and the double-blind method will minimize risk of biased study outcomes. The set study enrollment criteria, screening and baseline assessment, washout requirements and on-treatment conduct and assessment will minimize variables that could influence outcome except for that of the study drug being evaluated. The proposed study population as defined by the enrollment criteria will ensure a consistent sample and one that is largely representative of the broader patient population with NT1 and NT2. Combined these will enhance the generalizability of the study results.

The safety, dignity, and rights of study subjects predominate. It is thought that the proposed study design does not raise any ethical issues. The study is of appropriate duration for a chronic condition, there are no life-limiting effects from placebo, and study subjects can withdraw from the study at any time. This latter option will be made explicit during the informed consent process.

6.6 Potential Risks and Benefits

Based on early studies of FT218, it is possible to predict some of the discomforts and risks. The data suggest that the potential risks of FT218 are likely to be manageable and will be monitored like Xyrem. Clinical studies with Xyrem have yielded detailed information of its safety profile. Xyrem is approved by the FDA in the US and EMA for the treatment of subjects with narcolepsy. The potential risks of FT218 from PK studies in humans have been discussed in the

summary from the Phase 1 safety study (discussed in [Section 6.3](#)) and to date are consistent with and similar to what has been previously reported with sodium oxybate.

Clinical safety of Xyrem has been established and forms the basis for the FT218 safety plan. All causality and treatment-related events for Xyrem include: abdominal pain, diarrhoea, nausea, vomiting, fatigue, peripheral oedema, anorexia, dizziness, headache, abnormal dreams, confused state, nightmare, sleep walking and enuresis. The most commonly identified AEs for sodium oxybate are nausea, dizziness and headache. In terms of AEs where there was a dose response relationship, these AEs included nausea, vomiting, paraesthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking and enuresis. These events are most pronounced at the higher, 9.0 g dose, and in some cases related to the 7.5 g dose. The up-titration methods, as used with Xyrem, to maximum dose, are thus appropriate to establish safety and tolerability in study subjects who will participate in this clinical study.

The safety profile of Xyrem is thus well characterized. The safety profile, as described in the Xyrem approved labelling supports the safety of the FT218 study formulation. In addition, all necessary precautions and warnings related to subject self-care and self-monitoring for any signs and symptoms of respiratory or CNS depression, alcohol consumption, contraindicated medications, driving and use of heavy machinery apply to FT218. The proprietary extended-release oral suspension technology used for FT218 is well established. The technology is the same as that used for the marketed product Coreg CR (carvedilol, NDA 022012) for the treatment of hypertension, left ventricular dysfunction and mild to severe heart failure. This has been marketed in the US since 2007.

In addition to clinical safety and efficacy, consideration to the risk-benefit profile as it relates to abuse potential warrants careful consideration. Flamel Technologies has considered the wider risks of abuse potential. Data relating to drug abuse potential of illicit forms of GHB, sodium oxybate and related products with abuse potential, underwent extensive review by the World Health Organization (WHO) Expert Committee on drug dependence in 2012. At this meeting it was acknowledged that most GHB for abuse originates from clandestine manufacture and there was consensus on the associated narrow margin for safety. Outputs from Xyrem's risk evaluation and mitigation strategies postmarketing data were also evaluated. The finding showed minimal abuse or diversion of Xyrem. Clinical study supply and distribution methods for FT218 will adhere to regulatory and current Good Clinical Practice (cGCP) requirements. Within the clinical study framework a "closed system" of supply and distribution will be employed. Enhancement of this approach will be facilitated through implementation of study specific strategies to augment safety and mitigate abuse potential.

FT218 will provide a beneficial and alternative therapeutic strategy for subjects with narcolepsy. Sodium oxybate has a well characterized safety profile and is a known and established therapeutic choice among physicians for treating subjects with NT1 and NT2. Physicians are largely familiar with its use and application in clinical practice and the potential benefits of the sodium oxybate have been documented in the literature. The burden for the subject enrolled in this study is concentrated but not significantly greater than that which they experience during routine clinical practice for disease management.

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and International Council for Harmonisation (ICH) guidelines. Cognizant of FT218's designation as a Schedule I/Controlled Drug and associated safety risk profile and abuse potential, study specific risk mitigation strategies will underpin clinical roll-out of this clinical study.

7 STUDY OBJECTIVES

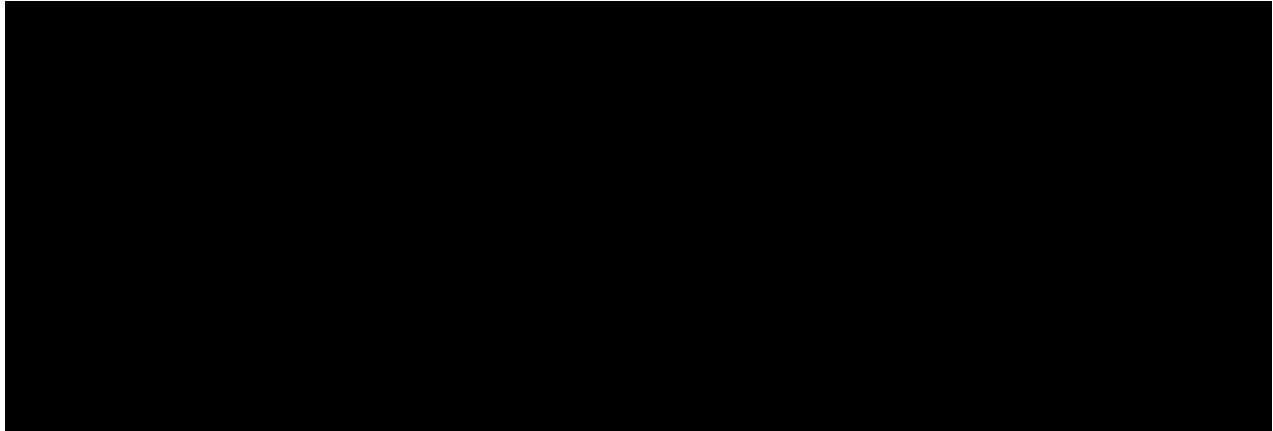
7.1 Primary Objective

The primary objective of the study is:

- To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating EDS in both NT1 and NT2 subjects as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT) and by the Clinical Global Impression (CGI) rating of sleepiness
- To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating cataplexy in NT1 subjects as measured by the number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary

7.2 Secondary/Exploratory Objectives

The secondary/exploratory objectives of the study are to compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo for the following outcomes:



7.3 Safety Objective

The safety objective of the study is:

- To evaluate the relative safety of FT218 compared to placebo.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

This is a Phase 3 double-blind, randomized, placebo-controlled, 2-arm clinical study. The purpose of this study is to assess the efficacy and safety of a once nightly formulation of sodium oxybate for the treatment of EDS and cataplexy in subjects with narcolepsy. Two populations of narcoleptic subjects will be studied in a single parallel group design: 1) NT1, and 2) NT2.

The study treatment period from screening to follow-up will last approximately 17 weeks. There is a 3-week screening period, followed by a central assessment of PSG and next-day MWT screening results (may take up to 3 days). If the subject is eligible, then randomization occurs. After randomization, dosing must start within 5 days (the window from randomization to dosing is to allow delivery of study drug to the site). There is a 13-week treatment period and a 1-week follow-up period. For subjects randomized to the active arm of the study the maximum duration of treatment with FT218 will be 13 weeks incorporating up-titration over a period of 8 weeks with 5 weeks on stable dosing at 9.0 g/night. For subjects randomized to placebo, there is no exposure to the study treatment.

The follow-up study visit will occur at least 1 week after the last dose of FT218 or placebo i.e. Period 4 (Visit 9, Week 15, Day 1 [+4/-0 i.e. a minimum of 7 days after the last on study dose]). Additional follow-up for safety surveillance and management will be done for unresolved AE/residual effects of FT218 study drug following last dose as determined by the study investigator and/or sponsor.

8.1.1 Study Design

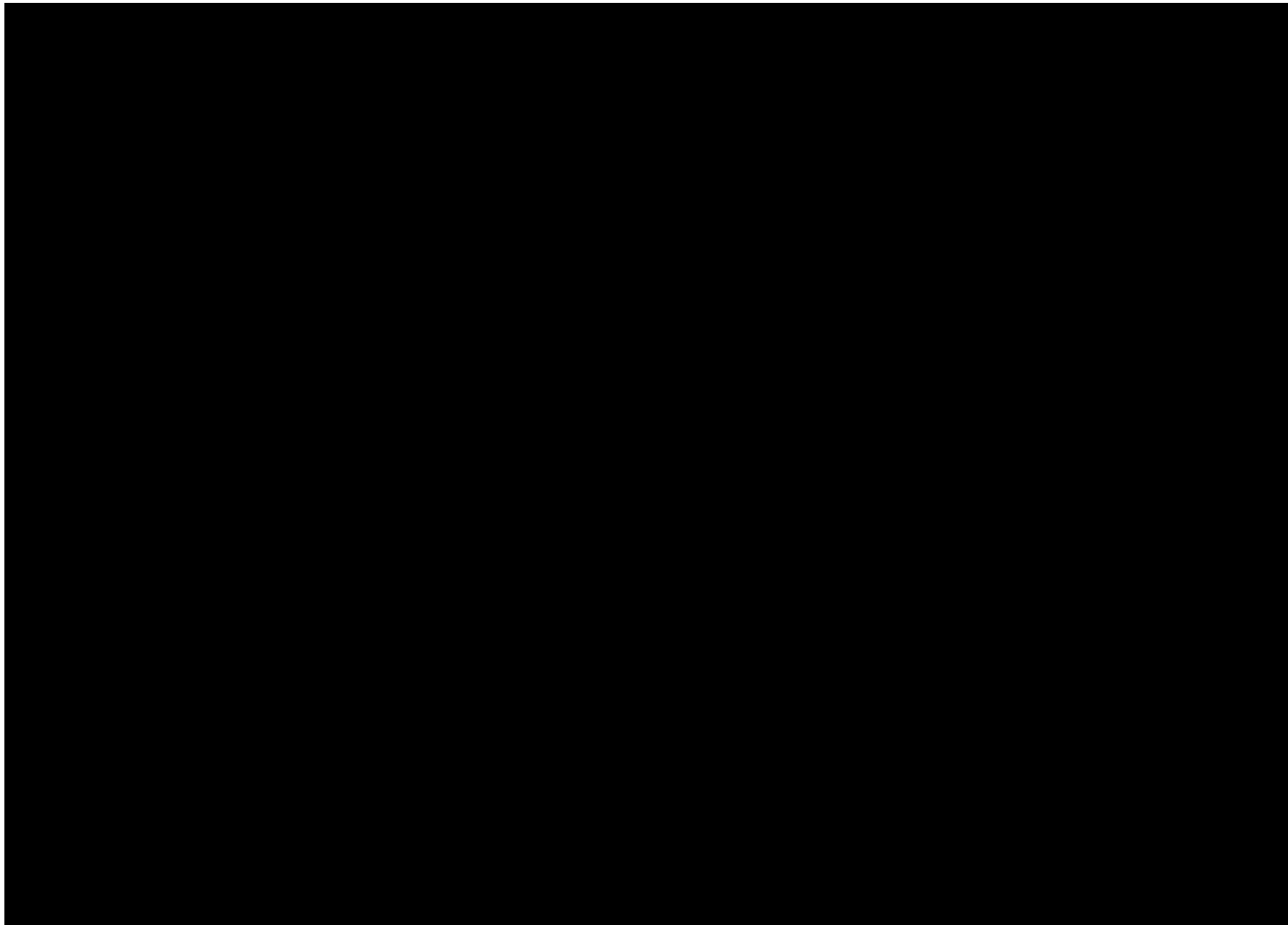
Screening and Baseline		Rand	Dose Titration				Dose Titration			Stable Dosing					EOS	FU	
										9.0g	9.0g	9.0g	9.0g	9.0g			
						7.5g	7.5g	7.5g	7.5g	7.5g	7.5g						
		Arm 1	4.5g	6g	6g												
		Arm 2	Placebo	Placebo	Placebo												
						Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo			
										Placebo	Placebo	Placebo	Placebo	Placebo			
Visit 1 W-3 D1	Visit 2* W-1 D7 W0 D1	EOSc +2 D	Visit 3** W1 D1	Visit 4* W3 D7	W4 D1	Visit 5 W6 D1	Visit 6* W8 D7	W9 D1	Visit 7 W11 D1	Visit 8* W13 D7 W14 D1	Visit 9 W15 D1						
<-----3-week washout----->																	
W-3	W0		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W15
Period 1	Period 2		Period 3a		Period 3b(i)		Period 3b(ii)		Period 3c(i)		Period 3c(ii)		Period 3c(iii)		Period 4		

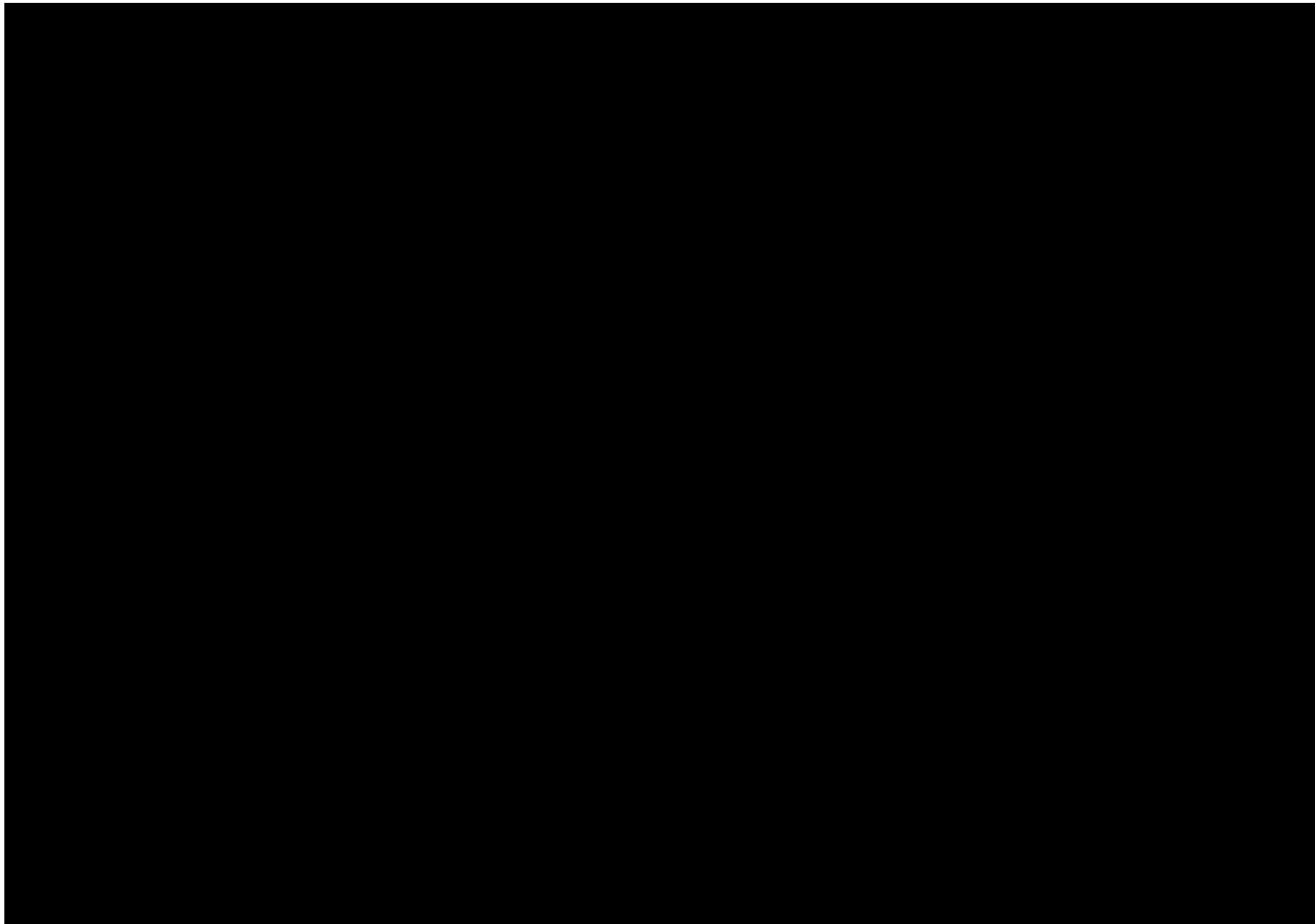
Abbreviations: D = day, EOS = End of Study, EOSc = End of Screening, FU = Follow-up, Rand = randomization, W = week, W/O = Washout

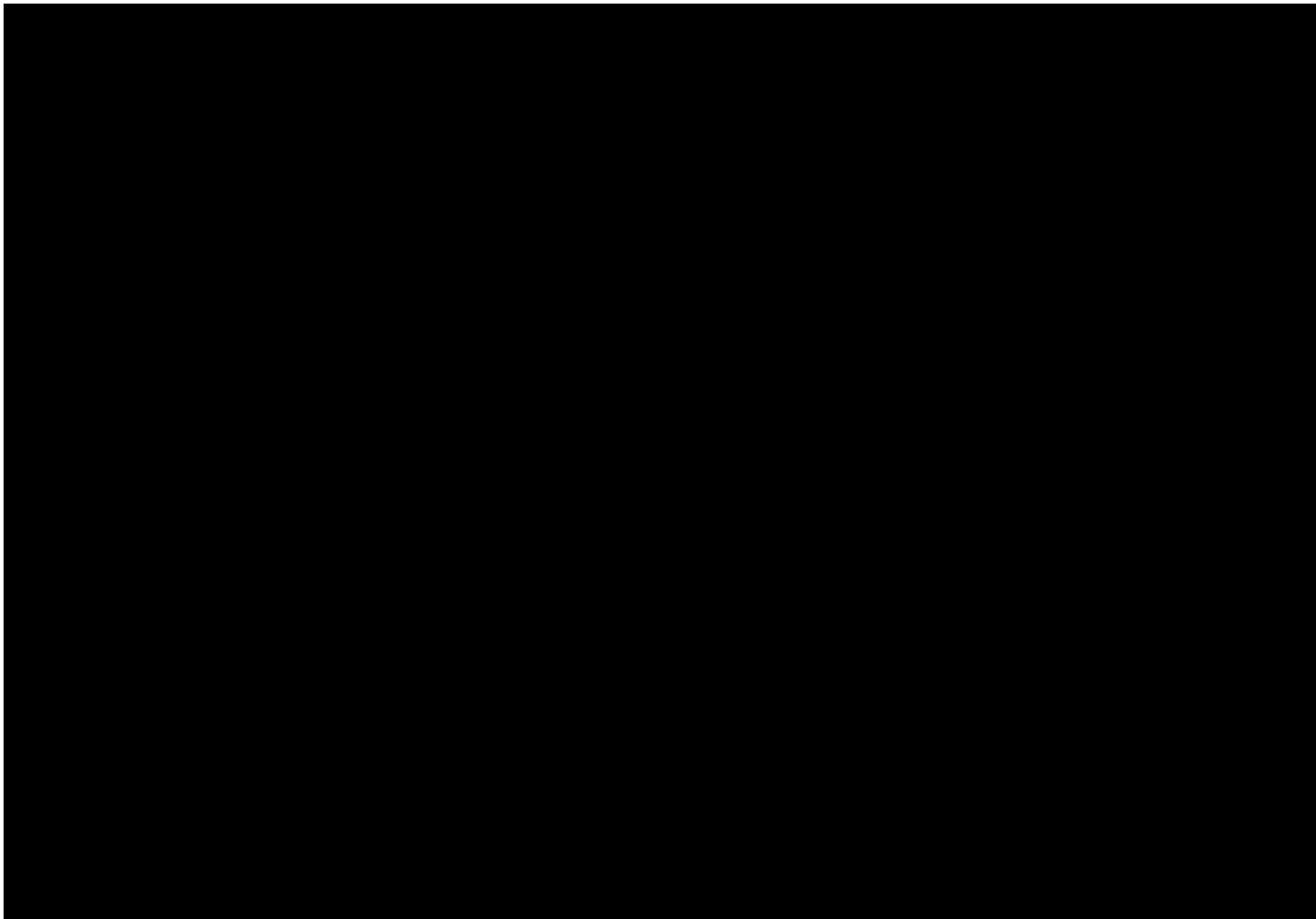
*Study visits where baseline assessment or full efficacy assessment are done extend into the following day and are thus indicated

**Up to 6 days is allowed between randomization (which occurs up to 2 days after the end of the screening period) and dosing to allow shipment of study drug to site. (Duration between end of screening period and dosing is no more than 7 days.)







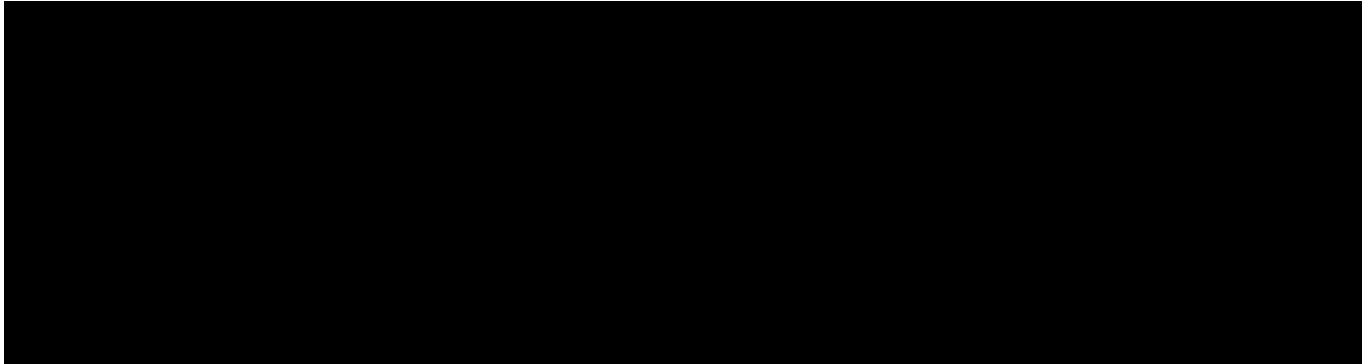


8.2 Discussion of Study Design

The rationale for the study design can be found in [Section 6](#).

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects



8.3.2 Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria at the screening assessment visit:

1. Male or female subjects 16 years of age or older
2. Willing and able to give written informed consent for study participation. For young adults (16 and 17 years old) who have not reached the age of majority they must be capable of giving assent and consent from a legally authorized guardian must be obtained, as required by local laws and regulations
3. Documented evidence of a diagnosis of NT1 or NT2 as, in part, determined by an overnight PSG and next-day MSLT with 2 or more SOREMPs with mean sleep latency in the pathological range i.e. < 8 minutes and meeting the NT1 and the NT2 as defined by the International Classification of Sleep Disorders -3 criteria¹¹
4. Current continuing presence of EDS as defined by subject report for the last 3 months and an ESS > 10
5. For NT1 only, current continuing presence of cataplexy as defined by subject report for the last 3 months
6. Subjects may use concomitant stimulants, but must comply with the following:
 - a. They must be on a stable dose of stimulants for at least 3 weeks prior to starting the screening process for this study; AND
 - b. They must use the same stimulant regimen throughout the entire study period, including during screening and posttreatment periods
 - c. They must discontinue all anti cataplexy drugs
7. Female subjects who:
 - a. Are postmenopausal for at least 1 year before the screening visit
 - b. Are surgically sterile, OR

- c. If of childbearing potential agree to practice effective double barrier methods of contraception, from the time of the signing of informed consent through the last dose of study drug, or agree to completely abstain from heterosexual intercourse
8. Willing and able to comply with all study mandated requirements and procedures for the duration of the clinical study
9. Willing to adhere to all study restrictions including:
 - a. Willingness to comply with the requirement to remain in bed for a minimum of 6 hours after taking the study drug
 - b. Adherence to concomitant drug washout requirements, as applicable, for the duration of the clinical study. Refer to [Section 8.4.8.1](#) for a list of all prohibited medications
 - c. Willing to refrain from operating a car or heavy machinery if determined necessary by the investigator or willingness to refrain from operating a car or heavy machinery for at least 6 hours after taking the nightly dose of FT218
 - d. Willing to abstain from alcohol for the duration of the clinical study
 - e. If a smoker, willing to abstain from smoking at night from approximately 9 pm to 7 am for the duration of the clinical study
10. Evidence of adequate support for the duration of the study, including transportation to and from the study site if needed

To be eligible for randomization, subjects must satisfy all of the following criteria:

1. Written informed consent obtained during the screening assessment visit
2. Still eligible as per requirements in [Section 8.3.2](#)
3. Compliance with drug washout requirements
4. Compliance in completing the study screening/baseline Sleep and Symptom Daily Diary. Compliance is defined as completing the diary at least 4 times in each of the screening weeks
5. Confirmation of EDS as defined by all of the following
 - a. Baseline ESS score > 10 points; AND
 - b. Baseline MWT mean sleep latency < 11 minutes following baseline PSG and as confirmed by the central scoring laboratory ([Section 11.12](#))
6. For NT1 only, current continuing presence of cataplexy as defined by an average of 8 reported cataplexy attacks per week in the screening/baseline Sleep and Symptom Daily Diary
7. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine test within 7 days prior to treatment

8.3.3 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criteria are applicable:

1. Prior use of sodium oxybate is allowed in the study but with the following exclusions:
 - a. Previous dosing must have been limited to no more than 4.5g per night
 - b. Patient should not have taken sodium oxybate for more than 2 weeks

- c. All previous dosing must not have occurred within the last year prior to entry to the study
2. Current use of sodium valproate
3. Any use of the following prohibited medications for the duration of the clinical study: (Section 8.4.8.1)
 - a. Anticonvulsants
 - b. Clonidine
 - c. SSRIs and serotonin and norepinephrine re-uptake inhibitors (SNRIs)
 - d. MAOIs
 - e. TCAs
 - f. Hypnotics
 - g. Anxiolytics
 - h. Sedating antihistamines
 - i. Antipsychotics
 - j. Other experimental medications designed to treat narcolepsy, cataplexy or any other condition
4. Treatment with any investigational products within 3 months before study enrollment
5. Any drug known to affect sleep-wake function. Concomitant stimulant use is permitted (Section 8.4.8)
6. A diagnosis of sleep apnea or any other sleep disorder known to cause EDS as determined by PSG and sleep history, including any PSG results indicating an apnea-hypopnea index (AHI) ≥ 15
7. The presence of any unstable or clinically significant medical and psychiatric disorders (as determined by medical or psychiatric history, physical examination, and/or clinical laboratory test) which in the opinion of the investigator may either put the subject at risk by participation in the study, or may influence the results of the study
8. Subjects with a previous history or current ideation of suicide attempt
9. Subjects who have a history of drug or alcohol use that, in the opinion of the investigator would interfere with study subject safety and adherence to study requirements
10. Required commercial or equivalent driving during the study period
11. An occupation that requires variable shift work or routine night shifts
12. Any travel across more than 3 time zones during the course of the study
13. Consuming more than 14 standard alcoholic drinks per week, on average, before participating in the clinical research study
14. Smoking during the night (approximately between 9 pm and 7 am) during the course of the study
15. Female subjects who are lactating or have a positive pregnancy test. Females of reproductive potential not willing or able to employ effective methods of birth control/contraception to prevent pregnancy for the duration of the study and for up to 1 week after completing study treatment
16. Any current malignancy and/or any history of malignancy within last 3 years
17. A history of seizure disorder, head trauma, or past invasive intracranial surgery
18. Subjects with severe chronic obstructive pulmonary disease. Subjects with mild to moderate chronic obstructive pulmonary disease and assessed as stable by the principal investigator (PI) are eligible

19. Principal investigator judgement on other underlying respiratory and/or other underlying condition or disorder that would potentiate risk of respiratory or CNS depression with concomitant use of sodium oxybate
20. Known hepatitis B surface antigen-positive status or known or suspected active hepatitis C infection
21. Known human immunodeficiency virus infection or acquired immunodeficiency syndrome related illness
22. Scheduled for procedures requiring general anesthesia during the study
23. Known contraindication/allergy/sensitivity/intolerance to the study drug, sodium oxybate, or the inactive ingredients of FT218 or placebo
24. Atrial fibrillation or an abnormal electrocardiogram (ECG) demonstrating clinically significant dysrhythmia(s)
25. Recent myocardial infarction or coronary revascularization (less than 3 months)
26. Uncontrolled hypertension
27. Known succinic semi-aldehyde dehydrogenase deficiency
28. Moderately or severely altered blood chemistry as defined by any one of the following:
 - a. A Cockcroft-Gault calculated creatinine clearance < 60 mL/min; OR
 - b. Liver function tests more than twice the upper limit of normal; OR
 - c. Serum bilirubin more than 1.5 times the upper limit of normal

8.3.4 Removal of Subjects From Therapy or Assessments

In accordance with the Declaration of Helsinki, subjects may withdraw consent to continued participation in the study at any time without giving a reason. This right will be respected without affecting the routine treatment or care of the subject. If the reason for withdrawal is volunteered by the study subject it will be recorded in the subject's medical notes and in the electronic case report form (eCRF). The Principal Investigator (PI) will ensure the protection of the study subject's interests is prioritized.

Study subjects must discontinue study drug and be withdrawn from the study for any of the following reasons.

- Withdrawal of consent by the subject
- Withdrawal of assent and corroborated by parent(s)/legal guardian
- Any medical condition that the PI or sponsor determines may compromise the study subjects safety by continuing to receive study drug
- Pregnancy
- An AE or SAE which requires discontinuation from study drug
- Inability to remain under medical observation for the duration of the study
- Clinical risk of emergent suicidal ideation
- Noncompliance to:
 - Study schedule
 - Sleep and Symptom Daily Diary completion requirements
 - Major deviation from protocol mandated procedures
 - Concerns over subject study drug handling in terms of subject safety, abuse, and/or dependence potential as determined by the PI

- Any other situation where, in the opinion of the investigator or the sponsor, continuation of the study would not be in the interest of the subject
- Lack of efficacy
- Discontinuation of the study by the sponsor
- Regulatory authority decision or change in Independent Ethics Committee (IEC)/Institutional Review Board (IRB) opinion for drug safety problems

Irrespective of reason for withdrawal or discontinuation the PI must record the reason for withdrawal (if subject initiated withdrawal, this information must be voluntarily given by the subject). All data available for the study subject at the time of withdrawal/discontinuation must be recorded in the eCRF, unless specified otherwise by the subject. The PI will request that the subject return all study drug and may request a follow-up visit especially if any adverse event(s) remain unresolved.

In the event a subject does not return for a scheduled visit after withdrawal, every effort should be made to contact the subject. This should be documented. Every effort to document subject outcome should be made.

PSG and MWT are at the discretion of the PI and consent of the subject. Early withdrawal study subjects will be followed for a week after the last dose of study drug. All SAEs and nonserious AEs assessed by the PI as related to the study drug should be followed to resolution or until the PI assesses them to be chronic or stable.

It will be left to the investigator's clinical judgement whether or not an AE is of nature, or severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what is perceived as an intolerable AE. If either of these occurs, the subjects must undergo an end-of-study assessment and receive appropriate care under medical supervision until symptoms cease or the condition becomes stable.

Withdrawal due to an AE should be distinguished from withdrawal due to lack of efficacy.

If the subject withdraws due to a SAE, the SAE must be reported in accordance with SAE reporting requirements.

Randomized subjects who have received at least 1 dose of study drug, who withdraw from the study prematurely will not be replaced.

8.3.4.1 Pregnancy

Study subjects may not be pregnant or nursing during the course of this study as indicated in the inclusion and exclusion criteria. Subjects of childbearing potential include all females who are not postmenopausal for at least 1 year before the screening visit and are not surgically sterile.

All female subjects of childbearing potential must agree to practice 2 effective methods of contraception, from the time of the signing of informed consent through the last dose of study drug or agree to completely abstain from heterosexual intercourse.

For all women of childbearing potential a serum pregnancy test will be performed at screening and a urine pregnancy test will be performed at least 7 days before commencing FT218/placebo dosing. The results must be available, documented and negative before the first dose of study drug is administered.

After study drug is dispensed at Visit 3, urine pregnancy tests will be repeated at each study visit throughout the remainder of the study, including the final study visit (Visit 9) or at the withdrawal visit if the subject withdraws from the study.

The investigator must report to the sponsor any pregnancy occurring in a study subject, during the subject's participation in this study. The study Pregnancy Reporting Form will be used. The report will be submitted within the same timelines as an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period after delivery.

Although pregnancy is not an SAE, and an elective abortion is not an SAE, any spontaneous abortion and/or any pregnancy that meets any regulatory serious criterion, or any pregnancy with an outcome for the pregnant person or the infant that meets regulatory serious criterion will be captured as an SAE.

8.4 Investigational Product

The active ingredient of FT218, sodium oxybate (GHB), is a CNS depressant. Drug product formulations containing GHB that have no marketing authorization are classified as Schedule I controlled substances within the US. For all non-US sites classification across regions can vary, local/regional classification will apply.

This study has been developed to ensure all local legal and regulatory requirements for the safe handling of Schedule I/Controlled Drug for all participating regions in the CLFT218-1501 clinical study are adhered to.

8.4.1 Investigational Products Administered

8.4.1.1 Definition of a Schedule I/Controlled Drug Substance

A substance where there is no current accepted medical use in treatment, a lack of accepted safety for therapeutic use under medical supervision and a high potential for abuse.

8.4.1.2 FT218 Study Drug Risk Management

The CLFT218-1501 operational framework will be structured to mitigate safety, abuse, misuse, and diversion risks associated with FT218. The framework will:

1. Safeguard subject safety and mitigate abuse, misuse, and diversion risks, and minimize potential for public-health risk through the implementation of best practice handling and distribution processes and procedures

2. Allow for robust evaluation of emerging safety data and FT218 study drug management for detection of risk in terms of subject safety, abuse, and misuse potential

8.4.1.3 Specification for Managing Controlled Substances

Systems and structures will be put in place to ensure compliance in the handling, distribution, prescription, and management of FT218. This will include:

1. A “closed system” of FT218 distribution
2. All study investigators and investigative site facilities will be assessed and qualified in advance of site set up. Only investigative sites meeting requirements will be qualified for participation in this clinical study. All qualified investigative sites will be monitored on an ongoing basis for the duration of the clinical study to ensure ongoing compliance with all legal and regulatory requirements as applicable to the FT218-1501 clinical study
3. Subject education on FT218 handling
4. Key investigator requirements include but are not limited to:
 - a. Authorization to prescribe the FT218 controlled substance by the jurisdiction in which they are licensed to practice
 - b. Evidence of current registration (Drug Enforcement Agency in the US, as per local/regional requirements for non-US sites) for the handling of the FT218 controlled substance
 - c. Complying with all FT218-1501 clinical study requirements and all legal and regulatory requirements specific to the safe handling and management of the FT218 drug product
 - d. Awareness of ramifications of noncompliance with requirements

All site specific approvals, registration forms and/or exemptions (if applicable for the latter) will be filed in the local study file at each site and a copy from each site will be provided for filing in the Trial Master File.

8.4.1.4 Drug Accountability

Sites must have the appropriate registration and authorizations to manage Schedule I/Controlled Drugs according to regional legal and regulatory requirements. Documented evidence of this authorization will be provided to the sponsor/designated contract research organization (CRO) before study site initiation.

Optimized study drug supply strategy is being applied to safeguard against loss, diversion, or theft of product.

All clinical drug supplies shipped to study sites will have clear instruction on-site requirements for receipt of drug, inspection of the shipment, confirmation or receipt, and storage requirements, all of which will be compliant with all applicable regional/local legal and regulatory requirements.

The FT218 pharmacy manual will be issued to each study site and will include detailed instruction as to applicable country and state level requirements including: inventory, storage, randomization, dispensing, dosing requirements, and returns processes to final disposition.

On receipt, clinical study material will be transferred to a secure location (appropriate for Schedule I/Controlled Drug). The PI/designee will inspect the shipment and enclosed temperature monitoring device to verify that clinical study materials were received in an acceptable condition and that the specified quantities have reached the study site. The PI/designee will complete and return all necessary paperwork as specified in the pharmacy manual.

Any quality issue, i.e. deficient clinical study material condition, appearance, documentation, labelling etc. either on shipment receipt or at any stage during the study must be reported. Necessary corrective actions will be identified and implemented as determined by the CRO/sponsor.

Upon receipt of FT218 study drug at site the PI/designee will check and document:

- Consistency of the FT218 study drug received against the shipping records
- Integrity of packages and seals
- Temperature records and temperature recording devices
- Receipt of associated documents as detailed in the study pharmacy manual

The PI/designee will file all related documentation and receipts to enable the tracking of product batches, shipping conditions and accountability in the study pharmacy file.

FT218 study drug must be stored as per protocol requirements and as per applicable legal, regulatory and labelling requirements. Details of storage requirements will be specified in the study pharmacy manual. Access to where study drug is stored must be restricted to preapproved personnel.

The location of the FT218 study drug will be recorded. FT218 study drug should not be moved from one storage location to another without prior approval from the CRO/sponsor. Full traceability of study drug storage must at all times be in place.

8.4.1.5 FT218/Placebo

FT218 study drug and placebo for each dosing period will be provided in a kit. Study drug will be provided as a powder in a sachet which will be of child proof quality. Each kit will contain the requisite number of study drug dose sachets. Sachet doses of 3.0 g and 4.5 g will be provided. Subjects will reconstitute to achieve the target dose levels, as necessary.

Treatment Arm 1

The treatment with FT218 is started with a gradual up-titration to stable dosing according to the following steps:

	Starting Dose × 1 week	Titration Dose × 2 weeks	Titration Dose × 5 weeks	Stable Dosing Period × 5 weeks
Arm 1	FT218 4.5 g (1 × 4.5 g sachet)	FT218 6.0 g (2 × 3 g sachets)	FT218 7.5 g (1 × 3 g sachet, 1 × 4.5 g sachet)	FT218 9.0g (2 × 4.5 g sachet)

Treatment Arm 2

The treatment with placebo is started with a sham gradual up-titration to sham stable dosing according to the following steps:

	Starting Dose × 1 week	Titration Dose × 2 weeks	Titration Dose × 5 weeks	Stable Dosing Period × 5 weeks
Arm 2	Placebo (1 × 4.5 g match sachet)	Placebo (2 × 3 g match sachets)	Placebo (1 × 3 g, 1 × 4.5 g match sachet)	Placebo (2 × 4.5 g match sachet)

8.4.2 Identity of Investigational Products

Test medication: FT218: Sodium Oxybate for Extended-Release Oral Suspension

Active substance	Sodium Oxybate
Strength	3.0 and 4.5 g sachets (for dosing at 4.5, 6.0, 7.5, and 9.0 g)
Dosage form	Powder for oral suspension
Manufacturer	Recipharm
Batch release	FLAMEL TECHNOLOGIES
Storage	Room temperature

Test Medication: Placebo

Substance	Inert constituents
Strength and Dose	Placebo; packaging and labelling will indicate doses as used in the active arm as per drug dosing schedule.
Dosage form	Powder for oral suspension
Manufacturer	Recipharm
Batch release	FLAMEL TECHNOLOGIES
Storage	Room temperature

8.4.3 Packaging and Labelling

Study drug management, handling, packaging, and labelling will comply with all applicable regional/local legal, regulatory, GxP regulations and sponsor requirements.

Active Drug: Arm 1:

A study kit will be provided to study subjects with enough study drug supply for the assigned dosing weeks. Active drug dose will be supplied in sachets. Two strengths will be supplied; 3.0 and 4.5 g, with the exception of the Week 1 dosing kit which will only contain a single dose strength of 4.5 g. Study subjects will be instructed on reconstitution methods according to their drug dosing regimen as predetermined by the drug randomization schedule. Each allocated drug kit will supply study subjects with enough drug until their next scheduled study visit for assessment and resupply. No oversupply will be provided.

Placebo Match: Arm 2:

Placebo kits and sachets will be identical in presentation and content feel to that of active drug. It will be labelled using the same strength dosages i.e. 3.0 and 4.5 g doses, with the exception of the Week 1 dosing kit, which will only contain a single dose strength of 4.5 g. Study subjects will be instructed on the reconstitution method identical to that of active study drug. Each allocated drug kit will supply study subjects with enough drug until their next scheduled study visit for assessment and resupply. No oversupply will be provided.

Specifications of Study Drug Quantities Supplied per Kit per Dosing Week.

Each study kit will provide enough study drug supply for the assigned dosing weeks. For weeks that require overnight PSG and next-day MWT, as part of the full efficacy assessment requirement, study kit supplies will be modified to allow for study sites to dispense a single night time dose to subjects at the PSG laboratory. Kit supplies for such weeks will contain enough study drug for 6 nights of dosing in the home setting. Study drug dose for night 7 will be dispensed at the PSG laboratory.

For all other weeks where there is no overnight PSG requirement study subjects will be supplied with the full quota of 7 nights drug supply for home dosing.

Details of the specifications of study drug supply quantities for each week of dosing are presented in [Appendix 17.2](#).

Labelling

FT218 and placebo will be dispensed to study subjects in a kit(s) containing study drug with sufficient drug supply to the next scheduled visit as detailed in [Appendix 17.2](#).

Labelling of both outer kit packaging and individual dosing sachets for both FT218 and placebo will meet with all legal and regulatory labelling requirements.

8.4.4 Method of Assigning Subjects to Treatment Groups

The drug dispensing strategy will, where feasible, minimize quantities of study drug stored at site at any one time. This will be mediated through a study specific interactive response technology (IRT) system (endpoint, San Francisco, US).

Once the overnight PSG and next-day MWT has been completed, the results will be reviewed and scored by a central scoring laboratory ([Section 11.12](#)). The targeted turnaround time for results following completion of MWT is ≤ 2 days. Results will be transmitted to the study PI.

Where possible, **on the same day** confirmation of subject PSG and MWT eligibility has been received from the central scoring laboratory and all other study entry criteria are met, the PI/designee will randomize the study subject.

All screening and baseline assessments confirming eligibility must be documented in advance of subject randomization to the double-blind study period. The PI/designee enters the information into the IRT system, and the appropriate study drug is sent to the site. This process may take up to 6 days.

The study site will notify all subjects of their eligibility status. Where a subject is eligible, the site will clarify requirements and arrange the first dispensing visit with the subject i.e., Visit 3.

1. Within 5 days of randomization where it took 2 days for the Central Scoring Laboratory to respond with the PSG/MWT eligibility response
2. Within 6 days of randomization where it took 1 day for the Central Scoring Laboratory to respond with the PSG/MWT eligibility response

As no oversupply of study drug will be provided. Study subjects will be reminded to adhere to the dosing schedule and assigned schedule of visits to the hospital/clinic. Periodically, electronic alerts via the ePRO systems will be sent to study subjects to promote compliance with the visit schedule and all drug handling and management requirements.

Following randomization, study subjects will be treated with their assigned study drug for a total of 13 weeks or until unacceptable AEs, withdrawal of consent or other treatment discontinuation criteria are met.

8.4.5 Selection of Doses in the Study

A description of the selection of doses for the study is provided in [Section 6.5](#).

8.4.6 Selection and Timing of Dose for Each Subject

Subjects will be instructed on the safe management of study drug within their residential setting.

All FT218 study drug must be kept out of reach from children and stored safely and securely to protect it from theft. It must be stored at 25°C with allowable excursions to 15°C to 30°C.

As food significantly reduces the bioavailability of sodium oxybate, study subjects will be instructed to take their nightly dose at least 2 hours after eating.

Study subjects will be instructed by study site staff on their nightly dosing regimen.

Guidance for Unused or Missed Doses

All doses of the study drug are intended to be taken as outlined in the protocol schedule. No doses should be missed or delayed due to subject visit scheduling and/or drug dispensing activities.

Reconstituted product should be taken on the night it is reconstituted. In the event that reconstituted drug is not used it must be stored securely and returned to the study site at the next visit. Any reconstituted but unused study drug should not be substituted for the following nights dosing.

Any missed nightly doses of the study drug are not to be taken, and the study drug for that night returned to the study site staff at the next study visit.

If there is a delay in taking the study drug or if the subject inadvertently falls asleep but wakes again prior to taking their study drug, a delayed start may be possible provided **both** the following criteria are met:

1. Study subjects feel awake enough to prepare and take the study drug as directed; and
2. Study subjects have a **minimum of 6 hours** left to sleep prior to waking up in the morning

In the event that fewer than 6 hours of possible sleep remain, subjects will be instructed to forego taking the study drug that evening. Subjects will be advised on reporting requirements for any deviation to the protocol mandated dosing regimen.

Study drug must be taken every night for the first week of study drug administration (Week 1) so that subjects are adequately prepared for the first up-titration at the end of that week. Thereafter, a maximum of 2 missed doses during each study period will be allowed. If, at any time, study subjects are not compliant with the study protocol dosing requirements, they may be withdrawn from further participation in the study.

Should study subjects become ill during the study, they should contact the study coordinator to discuss the decision surrounding taking the study drug.

If study subjects are too ill to take study drug on the night of PSG, the PSG will be scheduled for the following night. If this is not possible, or the subject remains ill the PSG for that period will not be done. In the event of a persistent AE and or where the study subject misses more than 2 doses of study drug in a single dosing period the subject will be assessed for potential withdrawal in conjunction with the sponsor.

8.4.7 Study Blinding and Unblinding Procedures

Provisions to ensure the integrity of the study blind include:

1. Provisioned drug product and placebo being identical in color, texture, taste, and appearance
2. All packaging being identical between groups (other than study randomization number allocation and kit number)
3. Labelling of FT218 study drug will preserve the double-blind integrity for the study
4. No biological tests being completed during the study risk inadvertent unblinding to study treatment allocation

To maintain the overall quality and integrity of CLFT218-1501 clinical study data, a code break will only occur in exceptional circumstances. Knowledge of the study subject's drug assignment would occur in circumstances where subject safety is at risk and knowledge of assignment is critical to the clinical management and safety of the subject.

In circumstances where unblinding is deemed to be necessary, the PI must first speak with the medical monitor. In case of emergency, or if the PI cannot reach the medical monitor, the PI will use his/her best clinical judgement, however, must notify the medical monitor as soon as possible. The PI will use the IRT system and/or the toll-free helpline for unblinding.

After unblinding of an individual subject, every effort must be made by the PI to maintain the blind as far as possible. The PI will not reveal the treatment allocation to the study subject nor any other personnel involved in the conduct of this study as far as possible. This includes other study site personnel, study monitors, the study CRO/sponsor or associated external parties involved in the running of the FT218 clinical study.

The PI will document in the subject's source documents and eCRF that the blind was broken but will not disclose the subject's drug assignment.

Where the study blind is broken for emergency, the subject will be withdrawn from the study. The early withdrawal visit will be completed and the End of Study (EOS)/Withdrawal eCRF form will be completed. Reason for withdrawal will be detailed code break and reason for code break will be documented.

8.4.8 Prior and Concomitant Therapy

All concomitant medications are to be taken as prescribed during the clinical study. All concomitant medications will be documented in both source documents and eCRF.

All medications (narcolepsy and non-narcolepsy), including washout medications, taken within 30 days of Visit 1 will be recorded in both source documents and eCRF at the screening and baseline visits. There will be ongoing recording of concomitant medications taken during the study.

Permitted concomitant medications are:

- a. Modafinil or armodafinil
- b. Methylphenidate
- c. Dextroamphetamine
- d. Methamphetamine
- e. Mixed salts amphetamines (Adderall, Vyvanse, etc.)
- f. Medications used to treat other diseases/conditions with mechanisms of action that do not influence sleep-wake function (i.e., insulin for diabetes or levothyroxine for hypothyroidism)

8.4.8.1 Prohibited Medication/Therapy

The following concomitant medications are prohibited during this study:

- a. Prior use of sodium oxybate s allowed in the study but with the following exclusions.
 - Previous dosing must be limited to no more than 4.5g per night
 - Patient should not have taken sodium oxybate for more than 2 weeks.

- All previous dosing must not have occurred within the last year prior to entry to the study
- b. Sodium valproate
- c. Anticonvulsants
- d. Clonidine
- e. SSRIs and SNRIs
- f. MAOIs
- g. TCAs
- h. Hypnotics
- i. Anxiolytics
- j. Sedating antihistamines
- k. Other experimental medications designed to treat narcolepsy, cataplexy or any other condition
- l. Antipsychotics

8.4.9 Treatment Compliance

Study subjects will receive training from study site staff who will have received protocol and study specific training from the CRO/sponsor. Site training will occur in the study set up period (i.e. at the investigator meeting and/or at the site initiation visit). Additional site training will be facilitated at study monitoring visits where appropriate via study manuals and guides.

Site staff will have documented training on the study protocol and will be aware of all requirements and advisory to give to study subjects and where applicable family members.

Site staff will be both capable and competent in clinical care management of subjects with narcolepsy and will be responsible for monitoring and advising subjects on the key safety risks associated with the FT218 drug product.

Study subjects will be informed on all requirements for the safe handling and self-administration of study drug. They will be both familiar and comfortable with its presentation, handling, and reconstitution. All training provided to study subjects must be documented.

Subject training will include:

1. Subject family members, where appropriate, will engage in the training process to allow for additional subject support in the home setting in both the drug reconstitution process and all of the safety, procedural and visit scheduling requirements for this study. The parent(s)/legal guardian of study subjects who have not reached the age of majority will be included in the study training process
2. Study subjects will be advised on the food requirement i.e. dosing at least 2 hours after the evening meal, and dietary salt restrictions, if applicable
3. Study subjects will be advised on best practice for study drug storage relative to their specific living arrangements. Site staff must be satisfied that study subjects have the necessary comprehension of what is required for study drug storage (both pre and post

reconstitution) and the necessary facilities, and contingency if away from their usual residence to store study drug safely

4. Study subjects will be advised on the potential side effects of study drug and will receive instruction on what to do in the event of a health-related emergency. Additionally, they will be advised on how and when to report such events to the site
5. Study subjects will be provided with emergency site contact numbers in the event of an emergency. To circumvent risk in the case of a health-related emergency all study subjects will be provided with an alert card with details of subject study participation with the FT218 sodium oxybate for extended-release oral suspension product. This card will flag that they are on a clinical study with a 1:1 chance that they are receiving a new extended-release oral suspension formulation of sodium oxybate. The contact details of the PI will be provided
6. Study subjects will be advised on rationale and importance of adhering to study restrictions
7. Subjects will be advised of what to do in the event of suspected loss or theft of drug product
8. Study subjects will be advised on study drug returns requirements. This will include detail on what to do with: 1) unused and unopened study drug, 2) what to do with reconstituted and unused study drug, 3) requirement for the return to site of all empty study drug sachets
9. Study subjects will be trained on using the ePRO device.

The site staff will assess subjects to determine the need for additional training at each study visit.

On return visit, the PI or designee will assess study subject compliance both verbally and by inventory of returns. All returns i.e. used, reconstituted and unused, and unopened study drug will be inventoried. Any deviation from dosing schedule will be documented and assessed for criteria for withdrawal.

9 TIMING OF STUDY PROCEDURES

Study subjects will receive study drug (FT218 or placebo) as outpatients. The study is divided into 4 sequential periods with a total of 9 required study visits. One in Period 1, one in Period 2, six in Period 3 (the double-blind period) concluding with a single follow-up visit in Period 4.

Where additional study visits are clinically required an unscheduled visit will be performed. A separate unscheduled eCRF visit module will be completed to record these visits. A set minimum of procedures to capture subject safety and progress will be done at the unscheduled visit, requirements for additional procedures will be determined by the PI/designee.

For early withdrawal, the EOS/Withdrawal eCRF module will be completed. In addition the EOS/Withdrawal eCRF page must be completed detailing the reason for subject withdrawal. The reason for withdrawal must also be recorded in the source documents.

Subjects will provide written informed consent as appropriate and according to local laws and regulations, before any study-related procedures are performed.



9.1 Pre-treatment – Periods 1 and 2

9.1.1 Period 1: Visit 1 (Week -3, Day 1) Screening and Assessment

Period 1 of the study commences with Visit 1. The purpose of this visit is to include subjects who meet the primary enrollment criteria for the study. All information collected will be clearly documented in the subject's medical notes. The following assessments will be performed:

- Complete informed consent procedures. Two originals of the subject information leaflet/informed consent and assent form, where applicable, must be collected. One will be given to the subject, one will be filed in the study site file, and a copy will be made and filed in the subject's medical note
- Record demographic data
- Assess for subject eligibility
- Collect full medical and surgical history. All baseline conditions will be recorded in the subject's medical notes
- Written confirmation of narcolepsy diagnosis by type i.e. NT1/NT2. A copy of all diagnostic records for narcolepsy, including, overnight PSG and next-day MSLT must be filed, and accessible to study monitors in the subject's medical notes. In addition, from historical PSG it must be confirmed that the subject did not have an AHI of ≥ 15
- Collect full psychiatric history
- Assess subjects for any prior or current drug abuse and dependence (which will exclude study subjects)
- Collect concomitant medications taken within 30 days of Visit 1. Specifically the following will be documented:
 - Confirmation that the subjects prior to sodium oxybate, if any, meets with the inclusion/exclusion criteria i.e. Prior use of sodium oxybate is allowed in the study but with the following exclusions:
 - a) Previous dosing must have been limited to no more than 4.5g per night
 - b) Patient should not have taken sodium oxybate for more than 2 weeks
 - c) All previous dosing must not have occurred within the last year prior to entry to the study
 - Confirmation that the subject has no current exposure to sodium valproate
 - Details of use of protocol prohibited concomitant medications: anticonvulsants, clonidine, SSRIs and SNRIs, MAOIs, TCAs, hypnotics, anxiolytics, sedating antihistamines, and antipsychotics within the last 30 days
 - Confirmation that the subject has not been exposed to any experimental medications designed to treat narcolepsy, cataplexy or any other condition within the last 3 months
- Obtain confirmation of subject's agreement to comply with the study washout requirements for prohibited medications for the duration of the clinical study
- Record subject alcohol, caffeine, and nicotine consumption (study restriction questions)
 - Obtaining confirmation of subject's agreement to abstain from alcohol for the duration of the study

- For smokers, obtain confirmation of subject's agreement to adhere to study mandated smoking restrictions for the duration of the clinical study
- Conduct screening C-SSRS (any current suicidal ideation or attempt will exclude subject)
- Conduct obstructive sleep apnea assessment, including measurement of subject's neck circumference and documentation of snoring patterns
- Perform complete physical examination
- Collect height (cm), weight (kg) and calculate body mass index (kg/m²)
- Record vital signs (systolic and diastolic BP, heart rate)
- Perform a 12-lead ECG after subject has been supine for 5 minutes
- Collect samples for hematology, biochemistry, hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus HCV antibody (HCVAb)
- Collect sample for serum pregnancy test (female subjects)
- Collect sample for urinalysis, and urine drug screen (includes benzodiazepines, cannabis, cocaine, opiates, and barbiturates)
- Administer ESS
- Provide ePRO device, and training and education on its use as it relates to study protocol diary records, drug adherence record and notifications and all other subject facing applications
- Explain Sleep and Symptoms Daily Diary completion. Inform subjects that for ongoing eligibility they must complete the Sleep and Symptom Daily Diary every day during Period 1 (every day for the 3-week period)
- Provide all necessary materials for participation including emergency site contact numbers advising subjects that they can contact the site at any time should they have any concerns or questions
- Schedule Visit 2 with overnight PSG and next-day MWT with the subject
- Update the IRT system with subject details and planned Visit 2 date

This visit marks the beginning of the washout period when prohibited concomitant medications are no longer permitted.

9.1.2 Period 2: Visit 2 (Week -1, Day 7) Baseline Visit

Following the screening visit, the second stage of subject assessment for continued eligibility will occur at the baseline visit i.e. Visit 2.

At this visit the PI/designee will firstly assess for:

- Confirmation of continued eligibility
- Compliance with drug washout requirements
- Assess compliance with alcohol consumption, abstinence from alcohol, and all other study restrictions (study restriction questions)
- Assess drug abuse and dependence. Clinical judgement to be exercised in determining need for performing additional urine drug screen for benzodiazepines, cannabis, cocaine, opiates and barbiturates at this visit

- Compliance in completing the screening/baseline Sleep and Symptom Daily Diary. Compliance is defined as completing the diary at least 4 times in each of the screening weeks.
 - Confirmation of continued presence of cataplexy (NT1 subjects only) as defined by an average of 8 reported cataplexy attacks per week as reported in the Sleep and Symptom Daily Diary
- EDS as defined by a baseline ESS score > 10 points

If these criteria are met the following assessments and procedures will occur:

- Review and record all concomitant medication
 - Assess for adherence to prohibited medication requirements
- Document any AEs
- Complete baseline CGI assessment of severity of sleepiness (by investigator)
- Administer baseline C-SSRS questionnaire
- Perform complete physical exam if determined clinically indicated by the PI
- Record vital signs (systolic and diastolic BP, heart rate)
- Collect samples for hematology and biochemistry
- Collect sample for urinalysis
- Perform urine pregnancy test (female subjects)
- Update the IRT system with planned Visit 3 date

If all assessments are satisfactory the study subject will then progress to having overnight 8-hour PSG with next-day 5 hour nap MWT. Results will be reported from the central scoring laboratory ([Section 11.12](#)).

9.1.2.1 Central Scoring Laboratory: PSG and MWT (+ 2 Days for results)

Once the overnight PSG and next-day MWT has been completed, the results will be reviewed and scored by a central scoring laboratory ([Section 11.12](#)). The targeted turnaround time for results following completion of MWT is ≤ 2 days. Results will be transmitted to the study PI.

Once confirmation of subject PSG and MWT eligibility has been received from the central scoring laboratory and all other study entry criteria are met, the PI/designee can randomize the study subject.

9.1.2.2 Randomization

Where possible, **on the same day** confirmation of subject PSG and MWT eligibility has been received from the central scoring laboratory and all other study entry criteria are met, the PI/designee will **randomize the study subject**. There is no clinic visit for randomization, i.e., the subject is not present at site.

All screening and baseline assessments confirming eligibility must be documented in advance of subject randomization to the double-blind study period. The PI/designee enters the information into the IRT system, and the appropriate study drug is sent to the site. This process may take up to 6 days.

Study treatment must begin:

1. Within 5 days of randomization where it took 2 days for the Central Scoring Laboratory to respond with the PSG/MWT eligibility response
2. Within 6 days of randomization where it took 1 day for the Central Scoring Laboratory to respond with the PSG/MWT eligibility response

The study site will notify all subjects of their eligibility status. Where a subject is eligible, the site will clarify requirements and arrange the first dispensing visit with the subject i.e., Visit 3.

The CRO/sponsor must be notified of any deviations to this. Deviations are to be documented.

9.2 Treatment Period – Period 3 (Dose Titration and Stabilization)

9.2.1 Period 3a: Visit 3 (Week 1, Day 1) Dose Titration to 6.0 g/Night

Period 3a will commence at Visit 3 with provision of the study drug to the subject. This marks the start of the double-blind period.

Dose titration steps for this period:

- Week 1: 1st week on study drug in this period: 4.5 g/night of FT218 or placebo
- Week 2: 2nd week on study drug: Increase dose by 1.5 g/night for a dosing regimen of 6g/night of FT218 or placebo
- Week 3: 3rd week on study drug: No dose increment - dosing regimen remains at 6.0 g/night of FT218 or placebo

The following assessments and procedures will be performed at Visit 3:

- Compliance with drug washout requirements
- Confirmation of continued eligibility
- Assess study restrictions compliance: (i) abstinence from alcohol, (ii) smoking restrictions, and (iii) all other study restrictions
- Assess drug abuse and dependence. Clinical judgement to be exercised in determining need for performing urine drug screen for benzodiazepines, cannabis, cocaine, opiates, and barbiturates
- Review and record all concomitant medication
 - Assess for adherence to prohibited medication requirements
- Document any AEs
- Administer “since last visit” C-SSRS questionnaire
- Perform physical examination if determined clinically necessary by the PI
- Perform urine pregnancy test (female subjects)
- Record vital signs (systolic and diastolic BP and heart rate)
- Collect weight
- Education & training and assessment of study subject on-study requirements and study drug reconstitution, compliance, management, prohibited medications, subject self-care and safety

- Dispense study drug
- Remind subject about instructions on Sleep and Symptom Daily Diary completion using the ePRO device

If the PI is concerned that the study subject will be unable to comply with FT218 study drug and study requirements following the training and education session the subject will be informed and withdrawn from study.

- Schedule Visit 4 with the study subject
- Update IRT system with subject's details for next visit

9.2.2 Period 3b(i): Visit 4 (Week 3, Day 7) Dose Titration to 7.5 g /Night

Dose titration steps for this period:

- Week 4: 1st week on study drug in this period: Increase dose by 1.5 g/night for a dosing regimen of 7.5 g/night of FT218 or placebo
- Week 5: 2nd week on study drug: 7.5 g/night of FT218 or placebo.

Visit 4 includes a full efficacy assessment (evaluation of the 6.0 g efficacy). Procedures at this visit include:

- Compliance with drug washout requirements
- Confirmation of continued eligibility
- Assess study restrictions compliance: (i) abstinence from alcohol, (ii) smoking restrictions, and (iii) all other study restrictions
- Assess for drug abuse and dependence. Clinical judgement to be exercised in determining need for performing urine drug screen for benzodiazepines, cannabis, cocaine, opiates, and barbiturates
- Assess compliance with drug handling, management, and safety requirements
 - Confirm subject is adhering to requirement to eat at least 2 hours before taking study drug
 - Subject re-education on study drug safety and handling and study-related procedures if deemed necessary by PI
- Review and record of concomitant medication
 - Assess for adherence to prohibited medication requirements.
- Document any AEs
- Collect CGI assessment of improvement in sleepiness (investigator blinded to MWT results)
- Administer "since last visit" C-SSRS questionnaire
- Perform physical examination if determined clinically indicated by the PI
- Record vital signs (systolic and diastolic BP and heart rate)
- Perform urine pregnancy test (female subjects)
- Review and confirmation of ePRO diary and questionnaire completion (on subject questioning and ePRO check).
 - Self-recorded study drug compliance record (with returns check)

- Compliance with Sleep and Symptom Daily Diary completion requirements for the past 3-week period. Completion of ESS (subject questionnaire)
- Overnight PSG
 - Next-day 5 hour nap MWT
- Dispense drug and perform accountability
- ePRO device handling and ePRO completion requirements and consequences of poor compliance will be discussed again with the study subject
 - Study subjects will be instructed to complete their Sleep and Symptom Daily Diary on a daily basis for the next 2 weeks

If the PI is concerned that the study subject will be unable to comply with FT218 study drug and study requirements following training and education session the subject will be informed and withdrawn from study.

- Schedule Visit 5 with the study subject
- Update IRT system with subject's details for next visit and study drug returns

9.2.3 Period 3b(ii): Visit 5 (Week 6, Day 1) 7.5 g/Night

There are no dose titration steps for this period:

- Week 6: 1st week on study drug: 7.5 g/night of FT218 or placebo
- Week 7: 2nd week on study drug: 7.5 g/night of FT218 or placebo
- Week 8: 3rd week on study drug: 7.5 g/night of FT218 or placebo

Visit 5 includes a partial efficacy assessment. Procedures at this visit include:

- Compliance with drug washout requirements
- Confirmation of continued eligibility
- Assess study restrictions compliance: (i) abstinence from alcohol, (ii) smoking restrictions, and (iii) all other study restrictions
- Assess drug abuse and dependence. Clinical judgement to be exercised in determining need for performing urine drug screen for benzodiazepines, cannabis, cocaine, opiates and barbiturates
- Assess compliance with drug handling, management, and safety requirements
 - Confirm subject is adhering to requirement to eat at least 2 hours before taking study drug
 - Subject re-education on study drug safety and handling and study-related procedures if deemed necessary by site PI
- Review and record of concomitant medication
 - Assess for adherence to prohibited medication requirements
- Document any AEs
- Complete CGI assessment of improvement in sleepiness (investigator blinded to MWT results)
- Administer "since last visit" C-SSRS questionnaire
- Perform physical examination if determined clinically indicated by the PI

- Record vital signs (systolic and diastolic BP and heart rate)
- Perform urine pregnancy test (female subjects)
- Review and confirmation of ePRO diary and questionnaire completion: (on subject questioning and ePRO check)
 - Self-recorded study drug compliance record (with returns check)
 - Compliance with Sleep and Symptom Daily Diary completion requirements for the past 2-week period. Completion of ESS (subject questionnaire)
- Dispense drug and perform accountability
- ePRO device handling and ePRO completion requirements and consequences of poor compliance will be discussed again with the study subject
 - Study subjects will be instructed to complete their Sleep and Symptom Daily Diary on a daily basis for the next 3 weeks.

If the PI is concerned that the study subject will be unable to comply with FT218 study drug and study requirements following training and education session the subject will be informed and withdrawn from study.

- Schedule Visit 6 with the study subject
- Update IRT system with subject's details for next visit and study drug returns

9.2.4 Period 3c(i): Visit 6 (Week 8, Day 7) Dose Titration to 9.0 g/Night, Stabilization

Dose titration and stabilization steps for this period:

- Week 9: 1st week on study drug in this period: Increase dose by 1.5 g/night for a dosing regimen of 9.0 g/night of FT218 or placebo
- Week 10: 2nd week on study drug: 9.0 g/night of FT218 or placebo.

This visit includes a full efficacy assessment (evaluation of the 7.5 g efficacy). Procedures at this visit include:

- Compliance with drug washout requirements
- Confirmation of continued eligibility
- Assess study restrictions compliance: (i) abstinence from alcohol, (ii) smoking restrictions, and (iii) all other study restrictions
- Assess drug abuse and dependence. Clinical judgement to be exercised in determining need for performing urine drug screen for benzodiazepines, cannabis, cocaine, opiates and barbiturates
- Assess compliance with drug handling, management and safety requirements
 - Confirm subject is adhering to requirement to eat at least 2 hours before taking study drug
 - Subject re-education on study drug safety and handling and study-related procedures if deemed necessary by site PI
- Review and record of concomitant medication
 - Assess for adherence to prohibited medication requirements
- Document AEs

- Complete CGI assessment of improvement in sleepiness (investigator blinded to MWT results)
- Administer “since last visit” C-SSRS questionnaire
- Perform physical examination if determined clinically indicated by the PI
- Collect vital signs (systolic and diastolic BP and heart rate)
- Perform urine pregnancy test (female subjects)
- Review and confirmation of ePRO diary and questionnaire completion: (on subject questioning and ePRO check)
 - Self-recorded study drug compliance record (with returns check)
 - Compliance with Sleep and Symptom Daily Diary completion requirements for the past 3-week period. Completion of ESS (subject questionnaire)
- Overnight PSG
 - Next-day 5 hour nap MWT
- Dispense drug and perform accountability
- ePRO device handling and ePRO completion requirements and consequences of poor compliance will be discussed again with the study subject
 - Study subjects will be instructed to complete their Sleep and Symptom Daily Diary on a daily basis for the next 2 weeks

If the PI is concerned that the study subject will be unable to comply with FT218 study drug and study requirements following training and education session the subject will be informed and withdrawn from study.

- Schedule Visit 7 with the study subject
- Update IRT system with subject’s details for next visit and study drug returns

9.2.5 Period 3c(ii): Visit 7 (Week 11, Day 1) Stabilization

Stable dosing:

- Week 11: 1st week on study drug in this period: 9.0 g/night of FT218 or placebo
- Week 12: 2nd week on study drug: 9.0 g/night of FT218 or placebo
- Week 13: 3rd week on study drug: 9.0 g/night of FT218 or placebo

Visit 7 includes a partial efficacy assessment. Procedures at this study visit include:

- Compliance with drug washout requirements
- Confirmation of continued eligibility
- Assess study restrictions compliance: (i) abstinence from alcohol, (ii) smoking restrictions, and (iii) all other study restrictions
- Assess drug abuse and dependence. Clinical judgement to be exercised in determining need for performing urine drug screen for benzodiazepines, cannabis, cocaine, opiates and barbiturates
- Assess compliance with drug handling, management, and safety requirements
 - Confirm subject is adhering to requirement to eat at least 2 hours before taking study drug

- Subject re-education on study drug safety and handling and study-related procedures if deemed necessary by site PI
- Review and record of concomitant medication
 - Assess for adherence to prohibited medication requirements.
- Document any AEs
- Collect CGI assessment of improvement in sleepiness (investigator blinded to MWT results)
- Administer “since last visit” C-SSRS questionnaire
- Perform physical examination if determined clinically indicated by the PI
- Collect vital signs (systolic and diastolic BP and heart rate)
- Perform urine pregnancy test (female subjects)
- Review and confirmation of ePRO diary and questionnaire completion: (on subject questioning and ePRO check)
 - Self-recorded study drug compliance record (with returns check)
 - Compliance with Sleep and Symptom Daily Diary completion requirements for the past 2-week period. Completion of ESS (subject questionnaire)
- Dispense drug and perform accountability
- ePRO device handling and ePRO completion requirements and consequences of poor compliance will be discussed again with the study subject
 - Study subjects will be instructed to complete their Sleep and Symptom Daily Diary on a daily basis for the next 3 weeks.

If the PI is concerned that the study subject will be unable to comply with FT218 study drug and study requirements following training and education session the subject will be informed and withdrawn from study.

- Schedule Visit 8 with the study subject
- Update IRT system with subject’s details for next visit and study drug returns

9.2.6 Period 3c(iii) Visit 8 (Week 13, Day 7) End of Study (EOS)

This visit includes a full efficacy assessment (evaluation of the 9.0 g efficacy).

- Compliance with drug washout requirements
- Confirmation of continued eligibility
- Assess study restrictions compliance: (i) abstinence from alcohol, (ii) smoking restrictions, and (iii) all other study restrictions
- Assess drug abuse and dependence. Clinical judgement to be exercised in determining need for performing urine drug screen for benzodiazepines, cannabis, cocaine, opiates and barbiturates
- Assess compliance with drug handling, management and safety requirements
 - Confirm subject is adhering to requirement to eat at least 2 hours before taking study drug
- Review and record of concomitant medication
 - Assess for adherence to prohibited medication requirements
- Document any AEs

- Complete CGI assessment of improvement in sleepiness (investigator blinded to MWT results)
- Administer “since last visit” C-SSRS questionnaire
- Perform full physical examination
- Collect weight
- Collect vital signs (systolic and diastolic BP and heart rate)
- Collect samples for hematology, biochemistry, and perform urine pregnancy test (female subjects)
- Collect sample for urinalysis
- Perform 12-lead ECG after subject is supine for 5 minutes
- Review and confirmation of ePRO diary and questionnaire completion: (on subject questioning and ePRO check)
 - Self-recorded study drug compliance record (with returns check)
 - Compliance with Sleep and Symptom Daily Diary completion requirements for the past 3-week period. Completion of ESS (subject questionnaire)
- Overnight PSG
 - Next-day 5 hour nap MWT
- Perform drug accountability and reconciliation
- Update IRT system with EOS details and final subject drug accountability
- Obtain ePRO device from subject and place in on-site safe storage
- Schedule follow-up visit with study subject

9.3 Follow-up Period – Period 4

9.3.1 Period 4: Visit 9 (Week 15, Day 1) Follow-up

A safety follow-up visit will take place at Week 15 Day 1 (+4/-0) when subjects have been off study drug for ≥ 1 week. Study procedures include:

- Review and record all concomitant medication
- Safety assessment: To include assessment for residual effects of study drug and all AE review.
 - All AEs including residual effects of study drug to be reported as per study protocol requirements. The outcome of any AEs with a date of onset during the double-blind period should be reevaluated and any new AEs should be recorded. All SAEs and nonserious AEs assessed by the PI as related to the study drug should be followed to resolution or until the PI assesses them to be chronic or stable
 - In the event that a study subject is unable to return to clinic for the follow-up visit, telephone contact with the study subject to assess for AEs and or residual effects of study drug and concomitant medications is expected.
- Perform physical examination if determined clinically indicated by the PI
- Collect weight
- Collect vital signs (systolic and diastolic BP and heart rate) if clinically indicated
- Collect samples for hematology or biochemistry if clinically indicated, and perform urine pregnancy test (female subjects)

- Discuss off-study narcolepsy therapeutic pathway with study subject

9.4 **Unscheduled Visits**

Where additional study visits are clinically required an unscheduled visit will be performed. Where an unscheduled visit leads to the subject's withdrawal, the procedures to be performed are those planned for the EOS visit as detailed in [Section 9.2.6](#).

Study procedures include:

- Compliance with drug washout requirements
- Confirmation of continued eligibility
- Assess study restrictions compliance: (i) abstinence from alcohol, (ii) smoking restrictions, and (iii) all other study restrictions
- Assess drug abuse and dependence. Clinical judgement to be exercised in determining need for performing urine drug screen for benzodiazepines, cannabis, cocaine, opiates and barbiturates
- Assess compliance with drug handling, management and safety requirements.
 - Confirm subject is adhering to requirement to eat at least 2 hours before taking study drug
 - Subject re-education on study drug safety and handling and study-related procedures if deemed necessary by site PI
- Review and record of concomitant medication
 - Assess for adherence to prohibited medication requirements
- Document any AEs
- Collect CGI assessment of improvement (investigator blinded to MWT results as applicable)
- Administer "since last visit" C-SSRS questionnaire
- Perform physical examination*
- Collect weight*
- Record vital signs (systolic and diastolic BP and heart rate)*
- Collect samples for hematology*, biochemistry*, and perform urine pregnancy test (female subjects)
- Perform 12-lead ECG after subject is supine for 5 minutes*
- Review and confirmation of ePRO diary and questionnaire completion: (on subject questioning and ePRO check)
 - Self-recorded study drug compliance record (with returns check) as applicable
 - Compliance with Sleep and Symptom Daily Diary completion requirements for the past period. Completion of ESS (subject questionnaire)
- Overnight PSG*
 - Next-day 5 hour nap MWT*
- Schedule next or follow-up visit with study subject if not withdrawing at this visit.

* At the PI's discretion

9.5 Duration of Treatment

The duration of treatment will be approximately 17 weeks. There will be a 3-week screening period, a 13-week treatment period, and a 1-week follow-up period.

Following the end of the subject's participation in the clinical study, no further study drug will be dispensed. The study PI will determine the most suitable medical care for the subject.

10 EFFICACY AND SAFETY VARIABLES

10.1 Efficacy and Safety Measurements Assessed

10.1.1.1 Maintenance of Wakefulness Test

The MWT is an evaluation used as a quantitative PSG measurement of daytime wakefulness/somnolence.²⁴ It shows whether or not a subject is able to stay awake for a defined period of time (90-minutes between one nap ending and the next one starting, spaced at 2-hour intervals throughout the day). Sleep latency is assessed by the amount of time it takes for subjects to fall asleep during the test. The MWT is an indicator of how well subjects may be able to function and remain alert during quiet times of inactivity.

10.1.1.2 Clinical Global Impression of Sleepiness

At Visit 2, the CGI assessment of severity of sleepiness scale will be conducted. At subsequent assessments, the CGI is evaluated on a 7-point scale, centered at No Change, and ranging from Very Much Worse to Very Much Improved. Subjects are rated by the qualified and approved evaluators who based their assessments on the severity of sleepiness at baseline.

10.1.1.3 Sleep and Symptoms Daily Diary

10.1.1.5 Epworth Sleepiness Scale

The ESS is intended to evaluate the extent of sleepiness in everyday situations by asking the subject a series of questions. In these questions, subjects are asked to rate their chances of dozing during each of 8 activities on a scale from 0 through 3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness.

10.1.2 Safety Assessments

10.1.2.1 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. Adverse events may include, but are not limited to the following: abnormal test findings, clinically significant signs and symptoms, hypersensitivity, any signs and/or symptoms from: drug overdose, drug administration/reconstitution error, any drug misuse, accidental exposure withdrawal, and or interactions, and exposure in utero.

Symptoms and signs of clinical and functional deterioration as defined in study efficacy assessment criteria for subjects with NT1 and NT2 will be not be captured as AEs. These signs and symptoms will be captured in the context of efficacy assessments via the ePRO enabled Sleep and Symptom Daily Diary, CGI rating of sleepiness, and on overnight PSG and next-day 5 hour nap MWT and will be reported as part of the efficacy analysis.

They include:

- Excessive daytime sleepiness
- Number of cataplexy attacks
- Disturbed nocturnal sleep
- Nightly arousals
- Sleep quality
- Refreshing nature of sleep
- Sleep paralysis

All other signs and symptoms of clinical and functional deterioration as they relate to the underlying diagnosis of narcolepsy (NT1 and NT2), study drug, and concomitant medications, or other will be recorded as AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be reported on the appropriate page of the eCRF.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

- Mild:** An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- Moderate:** An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed
- Severe:** An AE that prevents normal everyday activities; treatment or other intervention usually needed

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

For each recorded AE or SAE, the investigator or designee must make an assessment of causality based on the following criteria to determine the relationship between the AE and study drug:

Classification	Investigator's Judgement	Definition
Not Related: assigned when:	Not related	Where an AE or SAE is judged to be clearly and incontrovertibly due only to extraneous causes (e.g. disease, environment) and does not meet the criteria for study drug relationship listed under likely, possibly, or unlikely
	Unlikely	The AE or SAE is unlikely related to the study drug, when the AE or SAE (the first 2 criteria must be met): <ul style="list-style-type: none"> Does not follow a reasonable temporal sequence from administration of the study drug May readily have been produced by the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject Does not follow a known pattern of response to the study drug Does not reappear or worsen when the study drug is readministered
Related: assigned in any other cases when:	Possibly	The AE or SAE is possibly related to the study drug, when the connection to the study drug appears unlikely but cannot be ruled out with certainty. This causal relationship is assigned when the AE or SAE (the first 2 criteria must be met): <ul style="list-style-type: none"> Follows a reasonable temporal sequence from administration of the study drug May have been produced by the subject's clinical state, environmental, or toxic factors or other modes of therapy administered to the subject. Follows a pattern of response to the suspected study drug.

Related: assigned in any other cases when:	Related	The AE or SAE is considered related to the study drug, when the connection to study drug can be made with a high degree of certainty. This causal relationship is assigned when the AE or SAE (the first 3 criteria must be met): <ul style="list-style-type: none">• Follows a reasonable temporal sequence from administration of the study drug• Cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject• Disappears or decreases upon cessation or reduction in dose (note that there are important exceptions when an AE or SAE does not disappear upon discontinuation of the study drug, yet drug relatedness clearly exists [e.g. bone marrow depression or tardive dyskinesia])• Follows a known pattern of response to the suspect study drug• Reappears upon rechallenge
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If the investigator determines that the causality is unknown, the PI must then assign a causality of "Possibly" for the purposes of reporting. The causality must be clearly documented in the subject's medical notes and eCRF and report in accordance with the SAE reporting requirements if applicable.

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Concomitant medication
- Other, specify.

Adverse Event Outcome

The investigator will assess the outcome of the AE or SAE as follows:

- Fatal (the subject has died)
- Resolved (the AE or SAE has ended)
- Ongoing (the AE has not ended)*
- Unknown (lost to follow-up after repeated unsuccessful attempts to contact the subject)

* An AE outcome can only be categorized as ongoing if the AE is:

- Ongoing at the end of the reporting period: improved, stable or worsening
- Ongoing: improved, stable, or worsening, and referred to the subject's physician or a specialist.

Follow-up of Adverse Events

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Subjects should be followed for 7 days after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

Attention will be paid to the occurrence of AEs at all stages of the clinical study starting from signing of the informed consent to the follow-up visit which takes place 1 week after study completion or 1 week after premature withdrawal. Baseline events (i.e. medical history events that are ongoing) captured at the first study visit will only be recorded as AEs if during the screening and assessment period or double-blind period there is deterioration.

Information regarding all AEs, including SAEs, will be collected at each visit. All AE/SAEs that are encountered during the protocol specified AE/SAE reporting period will be followed to their resolutions, until the investigator assesses them as stable, or the subject is lost to follow-up.

Adverse events will be identified as treatment-emergent (TEAE) if the event occurs or increases in severity after the first dose of study drug is taken.

Adverse events considered related to study drug at the EOS or Early Withdrawal Visit (if applicable) will be followed until the subject is stable or the AE is resolved or the subject is lost to follow-up.

Adverse event data will be obtained at all study visits scheduled or unscheduled. Reporting will be based on information provided spontaneously by the subject and/or through questioning of the subject.

To elicit AEs, questioning at each study visit should begin with simple nonleading questions.

For example:

- How have you felt since your last visit?
- Have you had any health problems since you were here last?

Complete and appropriate data on all AEs experience (observed, volunteered or elicited) during the reporting period will be reported on an ongoing basis in the Adverse Event Form pages of the eCRF.

The following information regarding any AEs will be determined and documented by the investigator.

- Subject number
- The event (diagnosis preferred)
- The relationship of the AE to the study drug (causal relationship)

- Study drug information
- Seriousness (serious or not serious)

As the quality and precision of acquired AE data are critical, investigators will use the AE definitions provided in the protocol and will observe the following guidelines when describing adverse events in the Adverse Event Form pages of the eCRF.

- Whenever possible recognized medical terms will be used to describe AEs rather than colloquialisms (for example, “influenza” rather than “flu”) and abbreviations will be avoided
- Adverse events occurring secondary to other AEs (e.g. sequela or complications) will be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the eCRF. The investigator will provide his/her opinion of which is the primary AE

10.1.2.1.1 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that might have caused death if it had occurred in a more serious form)
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a preexisting nonworsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject’s ability to carry out normal life functions)
- Results in a congenital anomaly/birth defect

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Reporting of Serious Adverse Events

If a SAE occurs, the CRO/sponsor is to be notified within 24 hours of awareness of the event by the investigator. If the SAE is fatal or life-threatening, notification to the CRO/sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also

applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure in utero cases.

In the rare event that the investigator does not become aware of the occurrence of a SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere) the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to the CRO/sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the CRO/sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the SAE form. It will describe the SAE in enough detail to allow for a complete medical assessment of the case. Additional information concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the CRO/sponsor.

The SAE forms must be faxed **within 24 hours** for the attention of

INC Research Drug Safety
Fax No. +1 877-464-7787
e-mail: INCdrugSafety@INCResearch.com

The immediate SAE report will be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE.

Although the information required for completion of a SAE report form may not be available within the specified time period, an initial report should be submitted with the following information available.

- Subject ID (screening/randomization number)
- The suspect product/formulation – as blinded only the dose strength will be detailed
- An event or outcome that can be identified as serious
- The seriousness criterion
- The causal assessment (note: this may change as more information is learned, however, an assessment **MUST** accompany the original report)

All SAE information must be recorded on an SAE form and sent within 24 hours or 1 business day of learning of the report to INC Drug Safety. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on an SAE form and sent to INC Drug Safety. The SAE will be followed up until a final outcome and date are available. Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor/CRO will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the IEC/IRB approval/favorable opinion of the study. In addition, CRO/sponsor will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided in [Section 8.3.4](#).

Although pregnancy is not an SAE, and an elective abortion is not an SAE, any spontaneous abortion and/or any pregnancy that meets any regulatory serious criterion, or any pregnancy with an outcome for the pregnant person or the infant that meets regulatory serious criterion will be captured as an SAE.

10.1.2.1.2 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (e.g. investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The sponsor/CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the sponsor of such a case and that relevant follow up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the sponsor.

Warnings and Precautions

Safety Assessment to Exclude Obstructive Sleep Apnea

Sodium oxybate, when given to subjects with obstructive sleep apnea (OSA) will increase the risk of advancing sedation and respiratory depression. To support screening activities in ensuring subjects with OSA are detected and excluded as early as possible from the FT218 clinical study, a number of primary criteria will be assessed at Visit 1 to rule out OSA. Specifically, this will include taking the subject's neck circumference and documenting snoring patterns. These criteria will be assessed relative to ESS score, BMI, BP, age, and gender. A determination on eligibility to proceed through the screening period will be made relative to OSA risk. PIs will be trained on this at Site Initiation. In the event that following completion of the assessment the risk of OSA goes undetected, confirmation of the presence of OSA will be detected on overnight PSG (AHI \geq 15) at Week 3 in the screening and baseline period of the study. Where OSA is detected, the

subject will be withdrawn from study. Include any information relevant to safety (i.e., known side effects or treatment of potential side effects).

Safety Assessment of Suicidality

Study subjects will be assessed at study screening for suicidality using the C-SSRS. At risk subjects will be withdrawn. Risk for the emergence of suicidality, using the C-SSRS, will be assessed at each study visit for the duration of the clinical study. Where risk is identified, study subjects will immediately be withdrawn from study. The PI will implement the most appropriate medical and psychological care pathway to ensure subject safety and recover. Where a subject is withdrawn for suicidality this will be clearly indicated as the reason for withdrawal on the withdrawal form and in source data.

Safety Assessment for Abuse and Dependence

Subjects with a history of drug abuse and/or dependence will be assessed at the screening visit by the PI/designee. Subjects with a known and discernable history of abuse and/or dependence will be excluded.

Subjects will be assessed by the PI/designee for any signs and symptoms which may indicate an emergent abuse and dependence i.e. positive urine drug screen indicating concomitant use of contraindicated prescription drugs and/or illicit drug use, evidence or family report of concomitant use of alcohol with study drug product, suspicious claim(s) of lost product and looking for replacement study drug

10.1.2.2 Clinical Laboratory Evaluation

The hematology and biochemistry laboratory analyses will be performed at a central laboratory (ACM Global Central Laboratory, Rochester, US). Reference ranges will be supplied and used by the investigator to assess the laboratory data for clinical significance and pathological changes. The following laboratory safety tests will be performed:

Hematology

Hemoglobin, hematocrit, white blood cell count (total and differential), red blood cell count, platelet count, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration

Biochemistry

Creatinine, blood urea nitrogen, aspartate transferase, alanine transferase, gamma glutamyltransferase, alkaline phosphatase, total bilirubin, albumin, globulin, total protein, sodium, potassium, chloride, bicarbonate, estimated glomerular filtration rate, carbon dioxide, glucose, total cholesterol, triglycerides, and creatine phosphokinase.

Urinalysis

pH, glucose, ketones, blood, and protein by dipstick test at the central laboratory. If any of these parameters gives a positive result, a quantitative result will be transmitted.

10.1.2.2.1 Other Laboratory Variables

Drugs of Abuse Screening: Urine drug screen will comprise cocaine, benzodiazepines, cannabis, opiates, and barbiturates.

Serology: Hepatitis B surface antigen, and hepatitis C antibody

Pregnancy: serum β -human chorionic gonadotropin test will be performed at screening (Visit 1), urine β - human chorionic gonadotropin test at all other visits.

10.1.2.3 Vital Signs

Vital signs consisting of systolic and diastolic BP and heart rate will be recorded after at least 5 minutes in the sitting position.

10.1.2.4 Physical Examination

A complete physical examination including weight and evaluation of main body systems/regions, including: skin and mucous, ears/nose/throat, pulmonary, cardiac, GI, and neurological systems.

In case of abnormality, a comment will be recorded in the eCRF and subjects medical notes. Any deterioration in condition will be reported as an AE.

10.1.2.5 Electrocardiogram

Twelve-lead ECGs will be recorded after at least 5 minutes in the supine position.

Each ECG consists of a 10 second recording of the 12 leads simultaneously, leading to a 12-lead ECG (25 mm/s, 10mm/mV) printout with HR, PR, QRS, QT, QTc automatic correction evaluation, including date, time, initials and number of the subject, signature of the research physician, and at least 3 complexes for each lead. The ECG interpretation and values will be recorded in the eCRF.

10.1.3 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

11 STATISTICAL METHODS

Two subject populations, one with both narcolepsy symptoms and one with EDS will be studied in a single parallel group dose-escalation design. The treatments are placebo and increasing doses of the test drug, FT218. Two primary outcome measures, MWT and CGI quantify the treatment effect on EDS and the NCA is the primary outcome measure for cataplexy.

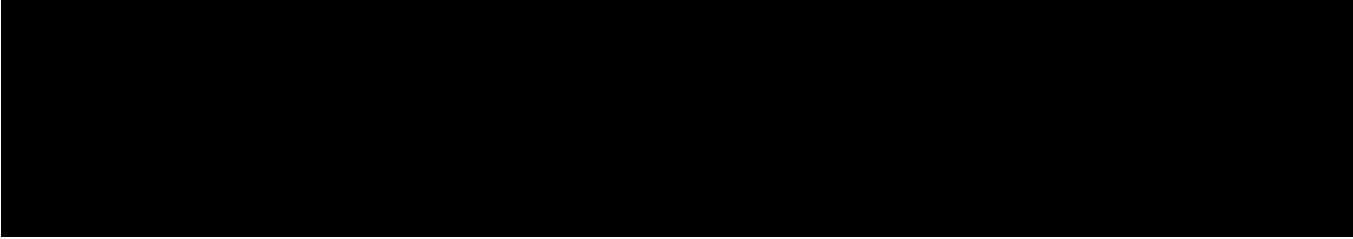
11.1 Statistical and Analytical Plans

The material in this section provides the basis of the statistical analysis plan (SAP) for this study. A complete SAP has been prepared to accompany this protocol for submission to the FDA for the Special Protocol Assessment. Details are provided therein.

11.2 Definition of the Analysis Populations

The target population is individuals in need of treatment of EDS and cataplexy in subjects with narcolepsy. The full analysis population for efficacy is the intent-to-treat (ITT) population including all randomized subjects with at least one efficacy measurement after receiving the 6.0 g dose (whether FT218 or placebo).

11.2.1 Determination of Sample Size



Estimation of sample size to achieve a desired power depends on the number and nature of the hypothesis testing paradigm and assumptions about the magnitude of the underlying effects. In this study, hypothesis testing will proceed in the following order. First MWT and CGI will be examined for statistical significance in the full sample including both NT1 and NT2 subjects for the 9 g dose. If significant, NCA for the same dose will be tested in NT1 subjects. If the first test fails, the data from this dose is not able to reject the null hypothesis of equality to placebo. If the first test is significant, but the second fails, the dose has been demonstrated to be superior to placebo for EDS treatment, but not for cataplexy. If both tests are statistically significant, the dose has been shown to be effective for both EDS and cataplexy treatment. The same sequence of testing will be followed for the 7.5 g and then the 6.0 g dose in a hierarchical manner.

Each outcome measure for the 9.0 g, 7.5 g and 6.0 g dose will be tested at the 2-sided α level of 0.05.

11.2.2 Randomization and Blinding



11.2.3 Interim Analysis and Unblinding

There are no planned interim analyses. Other than individual subjects being unblinded for safety issues, the database will remain blinded until after the database is locked.

11.2.4 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be appointed to review and assess study conduct and safety for the duration of the clinical study.

11.3 Analysis Sets

The ITT and per protocol (PP) populations form the bases for the evaluation of efficacy. The safety (S) population forms the basis for the evaluation of safety

11.3.1 Intent-to-Treat (ITT) Population

The ITT population includes all randomized subjects with at least one efficacy measurement after receiving the 6.0 g dose (whether FT218 or placebo). A valid diary measurement is defined to include at least 3 days of entries per week. Diary measurements with fewer days will be treated as missing, and if there are no other measurements, will not qualify the subject for the ITT population. Subjects will be assigned to treatment arms in the analysis as randomized.

11.3.2 Per Protocol (PP) Population

The PP population includes all subjects in the ITT population reduced by those who failed to follow the protocol with respect to protocol deviations. These are, inclusion or exclusion criteria not satisfied ([Section 8.3.2](#) and [Section 8.3.3](#)); deviations related to study drug administration, deviations to the schedule of visits and procedures, or deviations related to non-permitted concomitant medications ([Section 8.4.8.1](#)). Subjects will be assigned to treatment arms as randomized.

11.3.2.1 Safety (S) Population

The S population includes all subjects that receive at least one dose of study drug. Subjects will be assigned to treatment arms based on the treatment actually administered (FT218 if active drug was administered at any time, placebo otherwise).

11.4 Description of Statistical Analysis

The formal statistical analysis and specific dose/placebo contrasts will be based on a mixed-effects repeated measures model. Descriptive statistics characterizing the study population and the observed outcomes will be produced.

11.4.1 General Considerations

All statistical tests will be performed using a 2-tailed 5% overall significance level, unless otherwise specified. Descriptive statistics will be provided by treatment arm and as a summary across both treatment arms.

11.4.2 Use of Analysis Sets

For the primary statistical analysis of efficacy endpoints, the ITT will be used; a supportive analysis will be carried out on the PP population unless it is essentially the same as the ITT population, if the difference in sample sizes is less than 10%. All safety endpoints analysis will be conducted on the S population.

11.4.3 Analysis of Subgroups

The primary efficacy analyses of EDS will be performed on the ITT population. The primary efficacy analyses for cataplexy will be performed on the NT1 subgroup of the ITT population.

11.5 Subject Disposition

The number of subjects within each treatment arm of each analysis population will be summarized. The number of subjects entering each period of the study will be tabulated along with the number of subjects who withdraw. The timing of withdrawal and reasons for withdrawal ([Section 8.3.4](#)) will be summarized by treatment arm for each period of the study and summarized over all periods in the randomized stage.

11.6 Demographic and Other Baseline Characteristics

Subject demographics will be presented by treatment arm and for the total study. Baseline will be defined as the last measurement before randomization. Initial data at screening will also be reported for all screened subjects.

Cases for which the entry criteria or other protocol requirements were violated will be identified and their baseline characteristics will be summarized.

11.7 Medical History

Medical history data will consist of significant conditions or diseases recorded during the screening process. Data will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term for subjects in the S population.

11.8 Study Drug Exposure and Compliance

Study drug exposure and duration in the study will be derived based on first and last dose taken. Compliance will be computed as percentage of study drug taken.

11.9 Efficacy Analysis

11.9.1 Description of Primary Endpoints

The co-primary endpoints for evaluating EDS in both NT1 and NT2 subjects are the mean sleep latency on the MWT and the CGI. The MWT is the mean latency across 5 naps, averaged over the test day and the CGI is the clinician's global impression of improvement in daytime sleepiness from screening.

The primary endpoint for evaluating cataplexy is the NCA, which will be evaluated only in the NT1 subpopulation. The NCA is the mean number of cataplexy events recorded on the Sleep and Symptom Daily Diary during the period. Because of concern about the variability of this measure, a minimum number of diary entries of 3 per week will be required for the average to be considered an observation. If the number of days with entries is less than 3 per week, the mean NCA will be considered missing.

All ITT or PP subjects will be included in the evaluation of narcolepsy and all ITT or PP subjects with both conditions will be used in the evaluation of cataplexy.

11.9.1.1 Primary Analysis

A mixed-effects means model with repeated measures will be used to analyze change from baseline for each of the MWT and cataplexy endpoints. Each model will include treatment, time (at which the measurement was taken), treatment-by-time interaction, site and baseline score as fixed effects, and subjects as random effects. [REDACTED]

For CGI, a GLIMMIX model for binomial data with logit link will be used instead of a MMRM to analyze the categorized CGI response, i.e., proportion of patients who were very much or much improved. The observed values for the categorized response (very much or much improved versus other category) will be used as responses in the model. Each model will include treatment, time (at which the measurement was taken), treatment-by-time interaction and site as fixed effects and subjects as random effects. In fitting the model, time will range over the entire period of observations. The odds ratio, 95% confidence intervals for the odds ratio and p-value will be provided.

11.9.1.2 Sequential Testing Approach for Comparing FT219 and Placebo

The primary hypothesis tests of the efficacy of individual doses will be performed as contrasts within the mixed models. The hypothesis testing will proceed in the following order: first, to test

hypotheses for EDS, both MWT and CGI will be examined for statistical significance for the 9.0 g dose using the data collected during Period 3c(i), and 3c(ii). If both tests are significant, NCA for the same dose will be tested. If the first test fails (either MWT or CGI not significant), the data for the 9.0 g dose was not able to reject the null hypothesis of equality to placebo for either symptom. If the first test is significant (both MWT and CGI significant) but the second test (NCA) fails, the dose has been demonstrated to exceed placebo for EDS treatment but not for cataplexy. If both tests are statistically significant, the dose has been shown to be effective for EDS and cataplexy.

If the 9.0 g dose demonstrates efficacy for both EDS and cataplexy, the same sequence of testing will be followed for the 7.5 g dose using the data collected during Period 3b(i) and 3b(ii). If the 7.5 g dose demonstrates efficacy for both EDS and cataplexy, the same sequence of testing will be followed for the 6 g dose using the data collected during Period 3a.

Each dose will be tested at the 2-sided alpha level of 0.05. Efficacy tests for MWT and for CGI within a dose need not be adjusted, since both are required for demonstrating efficacy for EDS at that dose. Efficacy tests for NCA within a dose for demonstrating efficacy for cataplexy also need not be adjusted because the test is reached via a step down procedure. At each step, rejection terminates all subsequent hypothesis tests, which will be deemed to be non-significant. A strictly exploratory analysis examining secondary/exploratory endpoints is also proposed to provide evidence of consistency. The type I error rate for these endpoints will all be tested at the α level of 0.05.

Note: the testing of the efficacy of the 6.0 g dose is intended to address the question of identifying the minimally effective dose. If the 9.0 g dose and then the 7.5 g dose is effective on the primary outcome variables, hypothesis tests on the efficacy of the 6.0 g dose will be carried out.

11.10 Safety Analysis

Safety evaluation will be conducted on the S population and using the same evaluation period as for efficacy analysis.

Safety will be evaluated based on reports of AEs either spontaneously reported or observed in clinical laboratory analyses. They will be coded according to the MedDRA.

Adverse events will be summarized based on number and percentages of subjects with any AEs, SAEs, and permanent withdrawal from the study. Adverse events will also be tabulated by SOC and preferred term.

11.10.1.1 Laboratory Data

Laboratory data will be summarized in terms of the proportions of subjects with clinically relevant abnormalities using normal ranges. Shift tables will tabulate baseline to most extreme post baseline value. Summary statistics of raw data and change from baseline values, including means, medians, standard deviations, and ranges will be produced. Analyses will include all subjects in the S population who have had at least one laboratory test performed after the first study drug administration with an available baseline laboratory value. Baseline values will be measured as the last available measure before taking study drug.

11.11 Data and Safety Monitoring Board

An independent DSMB will be appointed to review and assess study conduct and safety for the duration of the clinical study.

This clinical study will be conducted in a double-blind manner. The DSMB comprises independent experts who will advise the sponsor and study investigator on matters relating to the safety and conduct of the clinical study. The DSMB will make recommendations to the sponsor and clinical study investigators about the continuation, modification or termination of the clinical study. To achieve this aim the appointed independent DSMB will periodically review and evaluate accumulated study data as they relate to study subject safety, study progress and conduct.

The DSMB will be governed by a charter which will define the deliberative processes of the group, including event triggers which would necessitate an unscheduled review, stopping rules, unblinding, and any voting procedures to initiate any data review. Confidentiality of internal discussions and activities will be upheld with a systematic reporting process to sponsor and dissemination process to all study investigators, IEC/IRBs and regulatory authorities as appropriate. The membership of the DSMB will reflect necessary clinical, scientific, and related disciplines necessary to interpret data from the clinical study to allow for full evaluation of study

subject safety. The DSMB will be blinded to treatment assignment with the exception of the unblinded biostatistician.

The composition of the DSMB will be laid out in the charter. No member of the DSMB should have direct involvement in the conduct of the study. In addition, no member will have financial, proprietary, professional, or other interests in Flamel Technologies that may affect impartial, independent decision-making by the DSMB.

11.12 Central Scoring Laboratory

At Visit 2 (Week -1, Day 7) a complete assessment for baseline efficacy parameters including an overnight baseline PSG and next-day MWT will be performed, after which a central scoring laboratory (Clinilabs, Inc New York, US) will confirm the eligibility of each subject. The central scoring lab will respond with its assessment within 2 days of receipt of PSG and MWT assessments.

The central scoring laboratory will have the necessary expertise and qualification to conduct PSG and MWT scoring.

11.13 Protocol Deviations

Protocol deviations will consist of: inclusion or exclusion criteria not satisfied ([Section 8.3.2](#) and [Section 8.3.3](#)); deviations related to study drug administration, deviations to the schedule of visits and procedures, or deviations related to nonpermitted concomitant medications ([Section 8.4.8.1](#)).

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to quality assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an informed consent form (ICF) and is administered study drug.

In accordance with eGCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

12.3 Data Management and Coding

The CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of the CRO.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use MedDRA for concomitant diseases and AEs and WHO Drug Dictionary for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

13 RECORDS AND SUPPLIES

13.1 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the CRO and the sponsor.

14 ETHICS

14.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

14.4 Informed Consent and Assent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

Young adults who have not reached the age of majority i.e. those who are 16 or 17 years of age, who meet the enrollment criteria are eligible to participate in this clinical study. The basic requirement of 21 Code of Federal Regulations (CFR) 50.20 applies, that is, 1) consent from their legally authorized representative must be obtained and 2) the assent of the young adult must be obtained. In obtaining assent, it must be determined by the PI that the young adult is of both intellectual and emotional ability to comprehend study requirements and implications.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be

given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and re consent will be obtained.

14.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act, applicable to national and/or local laws and regulations on personal data protection.

15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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17 APPENDICES

17.1 Investigator Signature Page

Protocol Title: A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

Protocol Number: CLFT218-1501

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Flamel Technologies and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Flamel Technologies and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Flamel Technologies, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Investigator Signature

Date

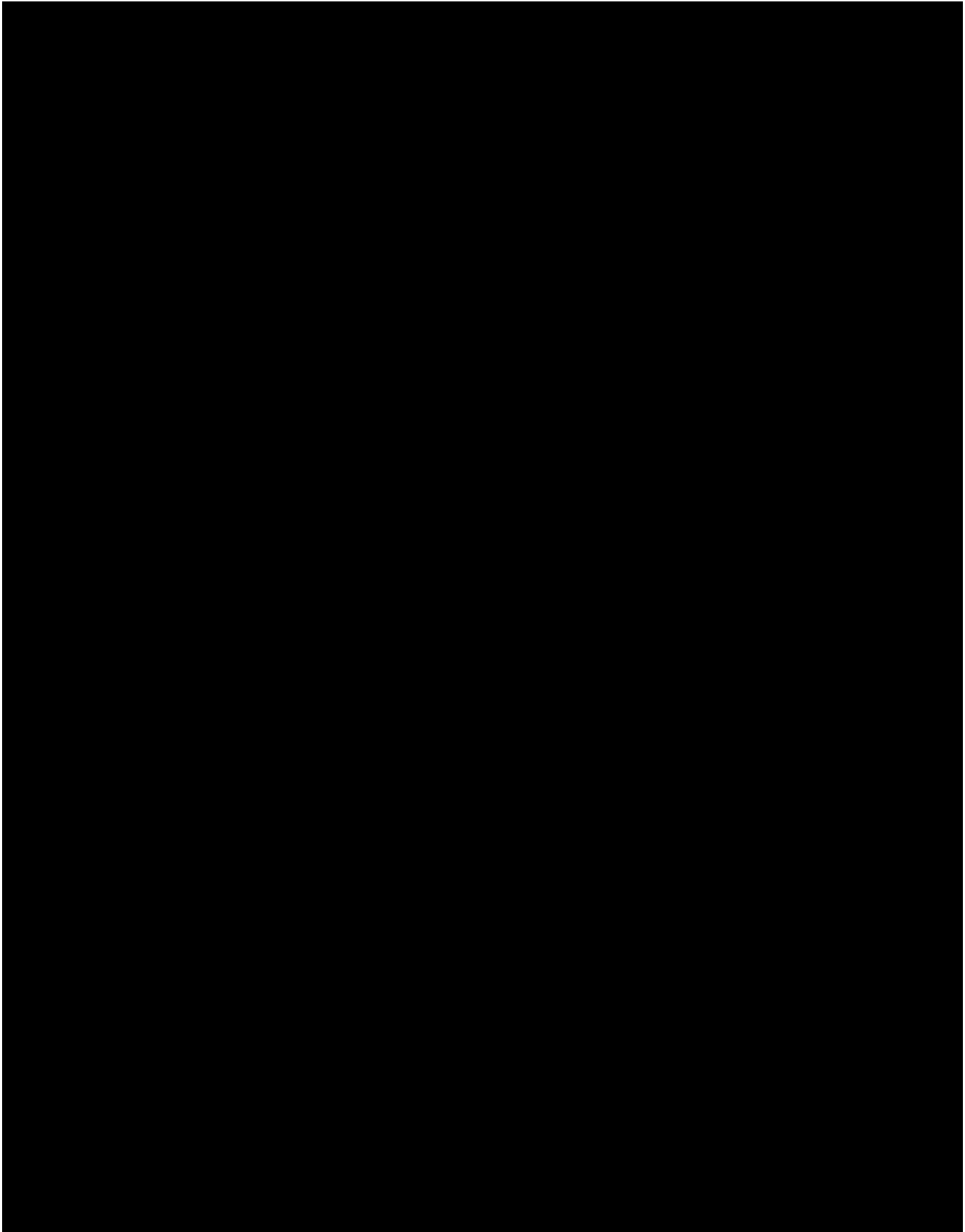
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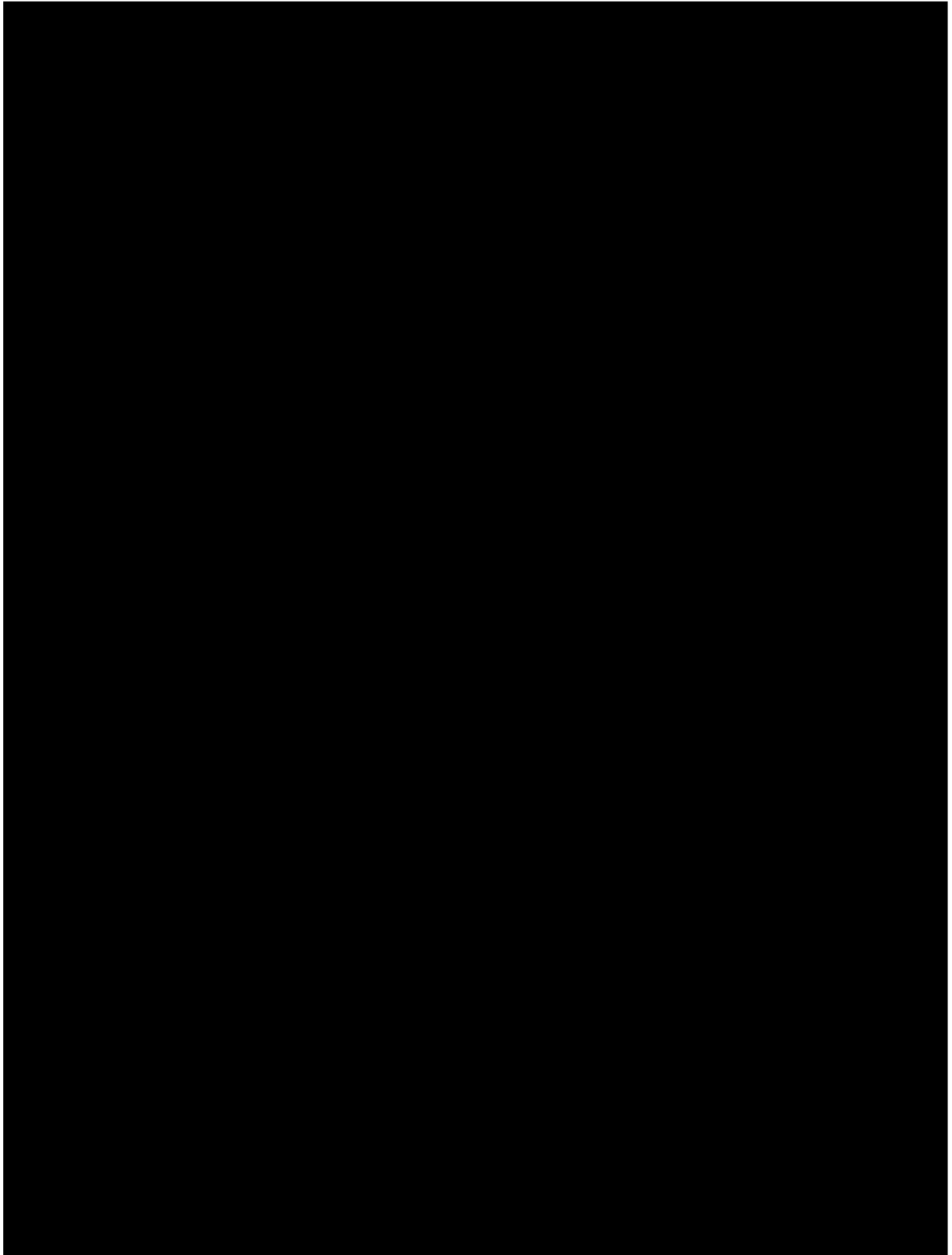
Institution

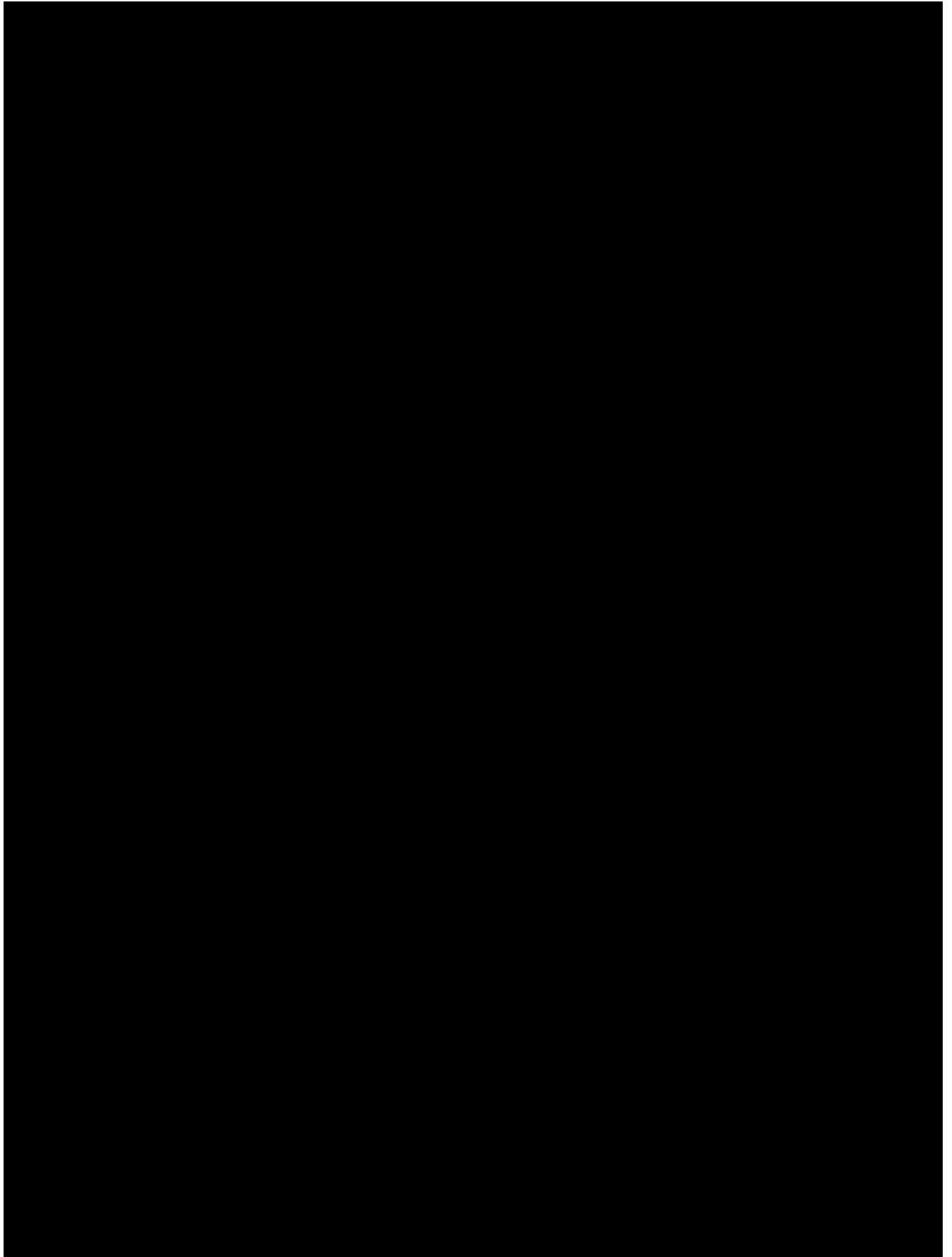
17.2 Study Drug Kit Dispensing

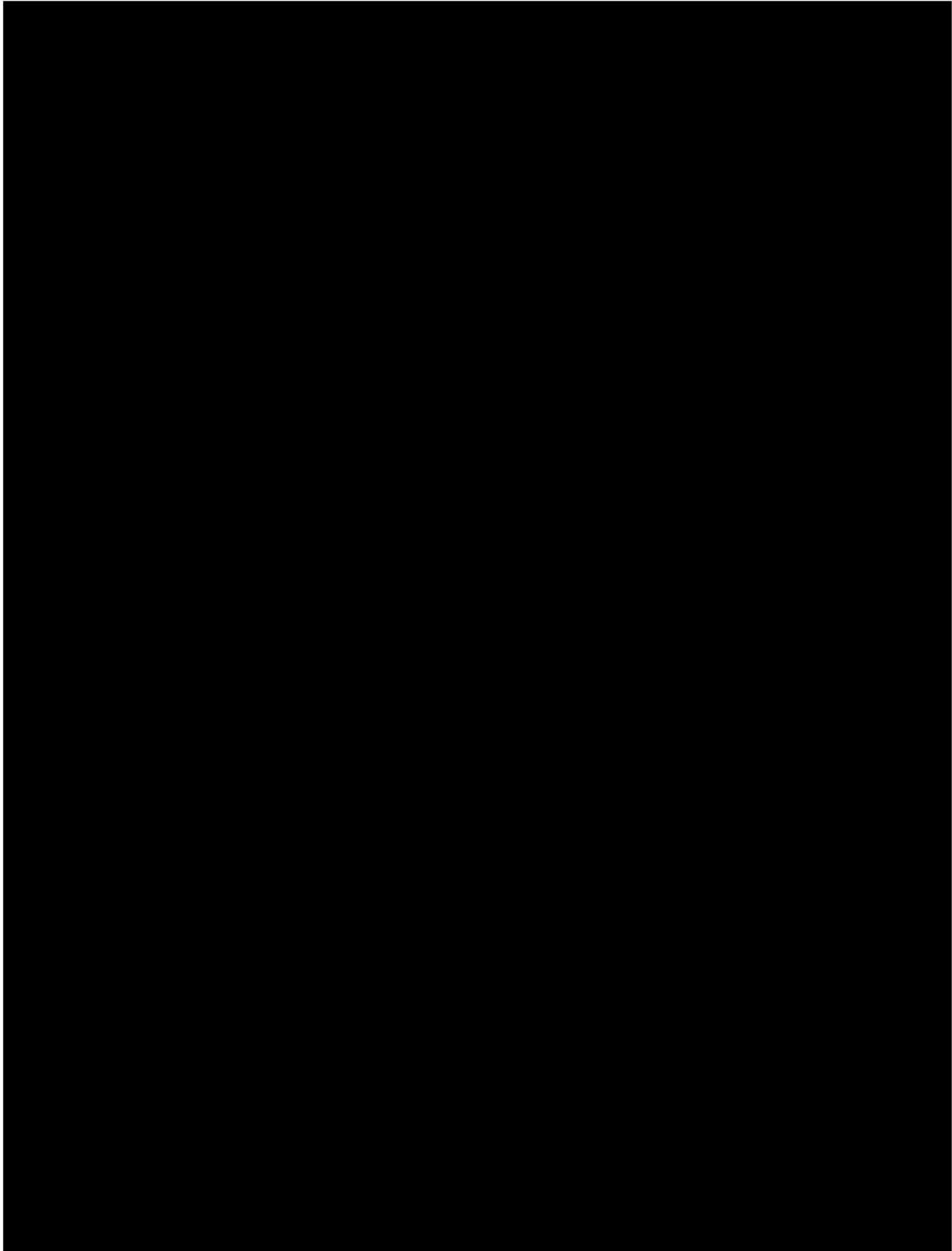
The table below details the specifications of drug supply quantities for each week of dosing for the duration of the study.

Dosing Week & Type	Dose Strength	Sachet Strength Dispensing	Efficacy Assessment Requirement	Drug Administration Specifications
Study Period 3a – Dose Titration				
Week 1	4.5 g	4.5 g (1 × 4.5 g/night) + dosing cup	Not for this week	Subject self-administration × 7 nights
Week 2	6 g	6 g (2 × 3.0 g/night)	Not for this week	Subject self-administration × 7 nights
Week 3	6 g	6 g (2 × 3.0 g/night)	Yes: on night 7 of Week 3 Full efficacy assessment – overnight PSG and next-day MWT	Subject self-administration × 6 nights. Night 7 Drug dispensed at clinic in advance of overnight PSG.
Study Period 3b(i) - Dose Titration				
Week 4	7.5 g	7.5 g (1 × 3 g/night, 1 × 4.5 g/night)	Not for this week	Subject self-administration × 7 nights
Week 5	7.5 g	7.5 g (1 × 3 g/night, 1 × 4.5 g/night)	Partial Efficacy Assessment	Subject self-administration × 7 nights
Study Period 3b(ii) – Dose Titration				
Week 6	7.5 g	7.5 g (1 × 3 g/night, 1 × 4.5 g/night)	Not for this week	Subject self-administration × 7 nights
Week 7	7.5 g	7.5 g (1 × 3 g/night, 1 × 4.5 g/night)	Not for this week	Subject self-administration × 7 nights
Week 8	7.5 g	7.5 g (1 × 3 g/night, 1 × 4.5 g/night)	Yes: on night 7 of Week 8 Full efficacy assessment -overnight PSG and next-day MWT	Subject self-administration × 6 nights. Night 7 Drug dispensed at clinic in advance of overnight PSG.
Study Period 3c(i) – Stabilization				
Week 9	9.0 g	9.0 g (2 × 4.5 g/night)	Not for this week	Subject self-administration × 7 nights
Week 10	9.0 g	9.0 g (2 × 4.5 g/night)	Partial Efficacy Assessment	Subject self-administration × 7 nights
Study Period 3c(ii) – Stabilization				
Week 11	9.0 g	9.0 g (2 × 4.5 g/night)	Not for this week	Subject self-administration × 7 nights
Week 12	9.0 g	9.0 g (2 × 4.5 g/night)	Not for this week	Subject self-administration × 7 nights
Week 13	9.0 g	9.0 g (2 × 4.5 g/night)	Yes: on night 7 of Week 13 Full efficacy assessment - overnight PSG and next-day MWT	Subject self-administration × 6 nights. Night 7 Drug dispensed at clinic in advance of overnight PSG.









17.4 Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.*

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5_1_eng-US081.doc

17.5 Columbia-Suicide Severity Rating Scale (C-SSRS) – Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;
Burke, A.; Oquendo, M.; Mann, J.*

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5_1_eng-USon.doc

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it". <i>Have you been thinking about how you might do this?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them". <i>Have you had these thoughts and had some intention of acting on them?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).		Most Severe
Most Severe Ideation: _____ <div style="display: flex; justify-content: space-between;"> Type # (1-5) Description of Ideation </div>		
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		_____
Duration <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts		_____
Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply		_____
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply		_____

SUICIDAL BEHAVIOR <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	Since Last Visit
<p>Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or Did you think it was possible you could have died from _____?</i> Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Has subject engaged in Non-Suicidal Self-Injurious Behavior? <input type="checkbox"/> <input type="checkbox"/></p> <p>Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted _____</p>
<p>Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted _____</p>
<p>Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Suicidal Behavior: Suicidal behavior was present during the assessment period? <input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Suicide: <input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Answer for Actual Attempts Only</p>	<p>Most Lethal Attempt Date: _____</p>
<p>Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech, first-degree burns, mild bleeding; sprains). 2. Moderate physical damage, medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>	<p>Enter Code _____</p>
<p>Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>	<p>Enter Code _____</p>

17.6 CGI-Severity (CGI-S) / CGI-Improvement (CGI-I)

CGI-Severity (CGI-S)

Considering your total clinical experience with this patient population, how sleepy is the patient at this time?

- 1. Normal, not at all sleepy
- 2. Borderline sleepy
- 3. Mildly sleepy
- 4. Moderately sleepy
- 5. Markedly sleepy
- 6. Severely sleepy
- 7. Among the most extremely sleepy patients

CGI-Improvement (CGI-I)

Compared to the patient's condition at BASELINE, this patient's condition is:

- 1. Very much improved
- 2. Much improved
- 3. Minimally improved
- 4. No change from baseline
- 5. Minimally worse
- 6. Much worse
- 7. Very much worse

17.7 Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

- 0 = would **never** doze
- 1 = **slight chance** of dozing
- 2 = **moderate chance** of dozing
- 3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading _____	—
Watching TV _____	—
Sitting, inactive in a public place (e.g. a theatre or a meeting) _____	—
As a passenger in a car for an hour without a break _____	—
Lying down to rest in the afternoon when circumstances permit _____	—
Sitting and talking to someone _____	—
Sitting quietly after a lunch without alcohol _____	—
In a car, while stopped for a few minutes in the traffic _____	—

THANK YOU FOR YOUR COOPERATION

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