NCT02192099

Study ID: GLYX13-C-203

Title: Open Label Extension for Subjects with Inadequate/Partial Response to Antidepressants during the Current Episode of Major Depressive Disorder Previously Treated with Rapastinel (GLYX-13) (Extension of GLYX13-C-202, NCT01684163)

Protocol Amendment 3 Date: 23 Nov 2016

Clinical Study Protocol

Protocol Number:	GLYX13-C-203
Study Drug:	Rapastinel (GLYX-13) Injection (rapastinel Injection)
FDA ID:	107,974
Clinicaltrials.gov:	
Title:	Open Label Extension for Subjects with Inadequate/Partial Response to Antidepressants during the Current Episode of Major Depressive Disorder Previously Treated with Rapastinel (GLYX-13) (Extension of GLYX13-C-202, NCT01684163)
Study Phase:	2
Sponsor:	Naurex, Inc, an affiliate of Allergan, plc.
Date:	Amendment 3 dated 23 November 2016 Replaces Amendment 2 dated 20 January 2015

INVESTIGATOR SIGNATURE PAGE

The signature of the investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol as specified in both the clinical and administrative sections, including all statements regarding confidentiality. This trial will be conducted in compliance with the protocol and all applicable regulatory requirements, in accordance with Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Principal Investigator

Printed Name	
Signature	Date

1 SYNOPSIS

Name of Sponsor Company	**Name of Finished Product**	**Name of Active Ingredient**
Naurex, Inc, an affiliate of Allergan, plc.	Rapastinel (GLYX-13)	[redacted]

Open Label Extension for Subjects with Inadequate/Partial Response to Antidepressants during the Current Episode of Major Depressive Disorder Previously Treated with Rapastinel (GLYX-13) (Extension of GLYX13-C-202, NCT01684163)

Study No: GLYX13-C-203

Planned Number of Investigational Sites: 10 US sites

Clinical Phase: Phase 2

Objectives

Primary Objective:

The primary objective of this study is to examine the safety of long term repeat exposure to rapastinel (GLYX-13) in subjects who participated in GLYX13-C-202.

The primary endpoint is the number of participants who experience an adverse event over the course of the study.

[redacted]

Methodology:

Study Design:

Phase 2 open label safety study of rapastinel (GLYX-13) for participants who completed 12 weeks of treatment in GLYX13-C-202 (NCT01684163).

At the screening visit, the Structured Clinical Interview for Depression (SCID) will be administered to determine whether any exclusionary conditions have arisen since subject's completion of GLYX13-C-202. [redacted] A physical examination will be conducted to ascertain if significant changes have occurred since the subject ended participation in GLYX13-C-202. Blood and urine samples will be obtained for laboratory analysis. Antidepressant agents used since the subject ended participation in GLYX13-C-202 will be recorded.

On Week 1 Day 1, subjects will arrive at the investigative site having fasted for at least 10 hours, with water as desired. Each subject's eligibility will be confirmed; then a physical examination will be performed, and blood and urine samples for laboratory analysis will be obtained. Vital signs will be assessed and mass recorded. ECG will be recorded, the [redacted]. Each subject will then receive an IV dose of rapastinel (GLYX-13) (225 mg or 450 mg unit dose) in a "slow bolus" injection in an upper extremity vein within approximately 1 to 2 minutes. Subjects will be discharged following determination by the investigator that they are medically able to leave.

Subjects will return to the study site during the first month on the schedule (weekly or biweekly) to which they were assigned in GLYX13-C-202. After the first month subjects will return to the study site on a

Name of Sponsor Company Naurex, Inc, an affiliate of Allergan, plc.	**Name of Finished Product** Rapastinel (GLYX-13)	**Name of Active Ingredient** L-threonyl-L-prolyl-L-prolyl-L-threonine amide, acetate salt

schedule defined by treatment plan set by the investigator. [redacted] Rapastinel (GLYX-13) will be administered. Subjects will remain in the study unit until determination by the investigator that they are medically able to leave the study unit.

At the last visit of each quarter, the [redacted] ECG will be recorded and blood and urine samples will be obtained for laboratory analysis. Rapastinel (GLYX-13) will be administered. Subjects will remain in the study unit until determination by the investigator that they are medically able to leave.

Dose Level

Unit doses of rapastinel (GLYX-13), 225 mg/3 mL or 450 mg/3 mL IV, will be administered in a "slow bolus" injection to each subject in an upper extremity vein within approximately 1 to 2 minutes. Investigator will begin treatment based on the dose level (5 mg/kg or 10 mg/kg) to which the subject was assigned during participation in GLYX13-C-202; subjects originally assigned to 5 mg/kg will receive 225 mg/3 mL, and subjects originally assigned to 10 mg/kg will receive 450 mg/3 mL. If subject experiences adverse event(s) that the investigator believes may be associated with rapastinel (GLYX-13), the investigator may decrease dose level from 450 mg to 225 mg. If at any point the patient cannot tolerate the minimum 225 mg unit dose, the patient should be discontinued from the study.

Dose Interval

Dose interval for the first month of participation will be that (weekly or biweekly) to which the subject was assigned during the randomized withdrawal phase of GLYX13-C-202. The investigator will then formulate a treatment plan in which dose interval will remain the same or change. The treatment plan may be modified from time to time by the investigator if it is deemed prudent based on subject's depression status.

Treatment Plan

Following one month at the dose level (subjects who were assigned to placebo during the randomized withdrawal phase of GLYX13-C-202 are eligible to participate and will begin at the dose level to which the subject was assigned during the stabilization phase of GLYX13-C-202) and dose interval to which the subject was assigned during the randomized withdrawal period of GLYX13-C-202, the investigator may continue the same dose level and dose interval, or may change the dose level and dose interval. The investigator will complete a treatment plan that outlines the dose level and dose interval at which rapastinel (GLYX-13) will be administered. The investigator, at the investigator's discretion, may change the treatment plan to alter dose level and/or dose interval based on the subject's depression status.

Subject Participation:

Participation in the study may continue until rapastinel (GLYX-13) is approved for marketing in the U.S. or until the study is ended by the Sponsor.

Number of Subjects Planned

It is planned to enroll up to 100 subjects who participated in clinical study GLYX13-C-202.

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

1. Participants who have completed 8 or more weeks of treatment in the preceding study (GLYX13-C-202, NCT01684163
2. Participants who wish to continue treatment with rapastinel (GLYX-13) after the

Name of Sponsor Company Naurex, Inc, an affiliate of Allergan, plc.	**Name of Finished Product** Rapastinel (GLYX-13)	**Name of Active Ingredient** L-threonyl-L-prolyl-L-prolyl-L-threonine amide, acetate salt

preceding study

3. Meets Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) criteria for major depressive disorder (MDD)
4. Female subjects of childbearing potential with a negative serum pregnancy test prior to entry into the study and who are practicing an adequate method of birth control (eg oral or parenteral contraceptives, intrauterine device, barrier, abstinence) and who do not plan to become pregnant during the course of the study. Female subjects may be included without a negative serum pregnancy test if they are surgically sterile or at least 2 years post-menopausal.
5. Clinical laboratory values <2 times the upper limit of normal (ULN) or deemed not clinically significant per the investigator and medical monitor
6. Ability to understand the requirements of the study, provide written informed consent, abide by the study restrictions, and agree to return for the required assessments
7. Based on the investigator and medical monitor's clinical judgment, subjects with eating disorders, obsessive compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), and generalized anxiety disorders secondary to major depressive episodes (MDEs) are permitted.

Exclusion Criteria:

1. Axis I diagnosis of delirium, dementia, dysthymia, amnestic or other cognitive disorder, schizophrenia or other psychotic disorder, bipolar I or II disorder, eating disorder (anorexia or bulimia nervosa), obsessive-compulsive disorder, panic disorder, acute stress disorder, agoraphobia, social phobia, attention-deficit hyperactivity disorder (ADHD), or PTSD
2. A clinically significant current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder
3. Experiencing hallucinations, delusions, or any psychotic symptomatology in the current episode; lifetime history of psychosis
4. Huntington's, Parkinson's, Alzheimer's, Multiple Sclerosis, or a history of seizures or strokes
5. Currently hospitalized or residing in an in-patient facility during study participation
6. Substance abuse since the end of participation in GLYX13-C-202, including greater than or equal to 5 units of alcohol per day where 1 unit = ½ pint of beer, 1 glass of wine 4 oz, or 1 oz. of spirits consumed most weeks or in the opinion of the investigator
7. Women who are planning to become pregnant during the course of the study
8. Allergy or intolerance to current antidepressant or other current medications
9. Participation in any clinical trial of an investigational product or device within 30 days of enrollment in this trial with the exception of GLYX13-C-202.
10. Positive screen for drugs of abuse: cocaine, marijuana, PCP, ketamine, opioid or other agent that in the opinion of the investigator is being abused
11. Pose current (past 6 months) suicide risk based on administration of the C-SSRS and the investigator's clinical judgment
12. Human immunodeficiency virus (HIV) infection (based on the based on the HIV-1 & HIV-2 antibody screen) or other ongoing infectious disease

Name of Sponsor Company	**Name of Finished Product**	**Name of Active Ingredient**
Naurex, Inc, an affiliate of Allergan, plc.	Rapastinel (GLYX-13)	L-threonyl-L-prolyl-L-prolyl-L-threonine amide, acetate salt

Test Product: rapastinel (GLYX-13) (150 mg/mL in water for injection)

Dose and Mode of Dosing:

IV Dosage:

- 225 mg dose in 3 mL with rapastinel concentration 75 mg/mL
- 450 mg dose in 3 mL with rapastinel concentration 150 mg/mL

Study drug will be administered in a "slow bolus" injection to each subject in an upper extremity vein within approximately 1 – 2 minutes.

Duration of Dosing:

Each subject will receive doses of rapastinel (GLYX-13) until ending participation in the study or until GLYX-13 is approved for marketing in the U.S.

Criteria for Evaluation:

[redacted]

Safety

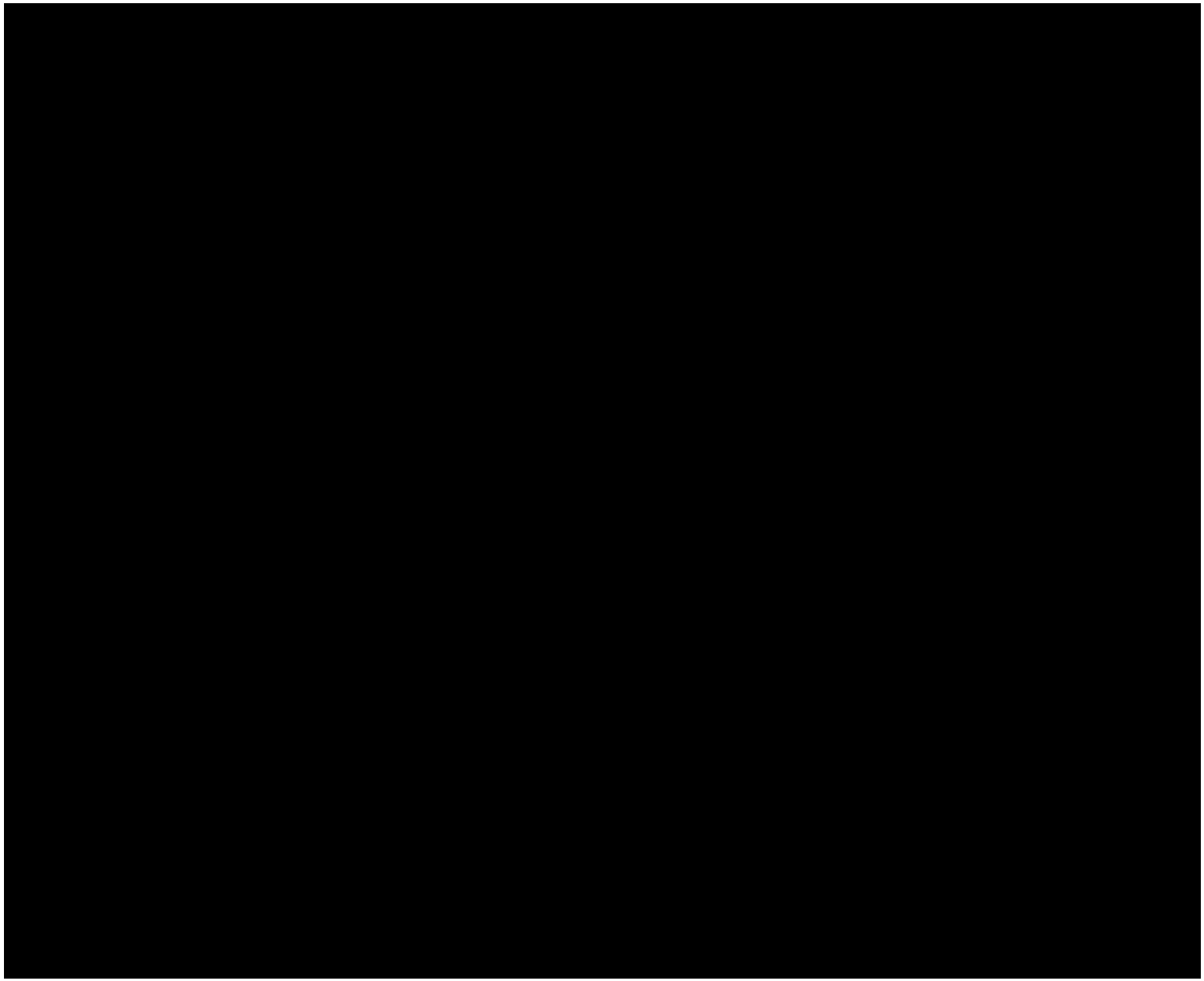
- [redacted]
- All reported AEs
- [redacted]

Statistical Methods and Data Analysis

Descriptive statistics will be presented for all efficacy and safety parameters. No inferential statistical analyses will be performed.

All safety parameters will be summarized for the Safety Population, defined as all subjects who received any injection of study drug.

Efficacy parameters will be summarized for the full analysis set (FAS), defined as all subjects who received any injection of study drug and who have at least one post-baseline efficacy assessment.



2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADT	Antidepressant treatment
ADHD	Attention-Deficit Hyperactivity Disorder
AE	adverse event
[redacted]	[redacted]
ATC	Anatomical Therapeutic Chemical Classification
[redacted]	[redacted]
CRF	case report form
CRO	Clinical Research Organization
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
DMID	Division of Microbiology and Infectious Diseases
DSM-IV-TR	Diagnostic and Statistical Manual, Fourth Edition, Text Revision
ECG	Electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
[redacted]	[redacted]
[redacted]	[redacted]
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IV	Intravenous
IWRS	interactive web response system
LSMs	least square means
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
MDEs	major depressive episodes
MTD	maximum tolerated dose
NaCl	sodium chloride
NCI	National Cancer Institute

NMDAR	N-methyl-D-aspartate receptor
NR2B	NMDA receptor 2B
PTSD	Post-Traumatic Stress Disorder
QID-SR	Quick Inventory of Depressive Symptomatology Self Report
Q-LES-Q SF	Quality of Life Enjoyment and Satisfaction Questionnaire Short Form
SAE	serious adverse event
SAP	Statistical analysis plan
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) of Mental Disorders
[redacted]	[redacted]

4 INTRODUCTION

The rationale for evaluating rapastinel (GLYX-13) in subjects with treatment-resistant depression results from recent studies using ketamine, a N-methyl-D-aspartate receptor (NMDAR) channel blocker, and CP-101,606, a competitive NMDAR antagonist. Both of these agents are efficacious in animal models and human diseases in which NMDAR have been implicated, but both suffer psychotomimetic effects that render them impractical to use for chronic therapy. When administered as single intravenous (IV) doses to subjects with treatment-resistant depression, the NMDAR antagonists ketamine [1] (channel blocker) and CP-101,606 [2] (NMDA receptor 2B [NR2B] competitive antagonist) induced significant, rapid antidepressant effects that lasted for several days following single doses, even though both of these agents, like rapastinel (GLYX-13), have short plasma half-lives. In subjects who received ketamine in a crossover study compared to placebo, improvement in depression scores was apparent at first assessment (40 minutes following dose); this improvement remained significant throughout the following week. Of 17 subjects treated with ketamine, 71% responded (> 50% reduction in depression score) and 29% experienced remission (depression score < 7) by 24 hours. At 1 week, 35% of responders maintained response following the single dose. Psychotomimetic effects were apparent at 40 minutes.

In a study in subjects who had failed paroxetine (the lead-in period of the trial), subjects who received a single intravenous (IV) dose of CP-101,606 showed improvement in depression scores compared to placebo at Day 5 (primary endpoint). Of 15 subjects treated with CP-101,606, 60% responded, and 33% experienced remission. Of responders, 78%, 58%, 42% and 30% maintained response on Days 8, 12, 15, and 30. Psychotomimetic effects were observed in many of the subjects who received CP-101,606. Thus, single IV doses of ketamine or CP-101,606 caused rapid, sustained reductions in depression despite plasma half-lives of 2 hours.

These studies are particularly interesting from the perspectives of medical need and commercial opportunity since the onset of action of existing antidepressant drugs is 2 weeks or longer and about one-half of subjects do not achieve a response to the first drug tried. About 30% of subjects do not respond to any of multiple drugs tried. In contrast, ketamine and CP-101,606 both produced responses in most subjects, even though all of these subjects had failed at least 2 other antidepressant drugs. Further, the onset of antidepressant action was rapid, within hours

for ketamine. Either of these effects in a drug that can be used therapeutically (neither ketamine nor CP-101,606 can be due to their psychotomimetic side effects) would be an advance in therapeutics.

Rapastinel (GLYX-13) is an NMDAR glycine site functional partial agonist.[3] IV administration of rapastinel (GLYX-13) results in rapid antidepressant-like activity in the Porsolt assay in rats without changes in locomotor activity or inhibition of prepulse inhibition that predict psychotomimetic side effects in humans.[3] In rats and normal human volunteers, rapastinel (GLYX-13) exhibits plasma half-life of less than 10 minutes following IV administration. In a phase 2a study (GLYX13-C-201) in subjects with MDD who had failed (< 25% improvement using the ATRQ) at least one antidepressant agent during the current episode in whom all

antidepressant agents had been washed out for 14 days, a single IV dose of rapastinel (GLYX-13), 5 mg/kg or 10 mg/kg, reduced [redacted] compared to placebo within one day and activity lasted for 7 days, but not 14 days.[7] Psychotomimetic side effects assessed using the BPRS+ scale were not observed in any subjects.

This protocol will now explore fixed IV doses of 225 mg (to replace 5 mg/kg) and 450 mg (to replace 10 mg/kg). In previous studies, rapastinel (GLYX-13) has been studied at dose levels up to 30 mg/kg IV and was found to be well tolerated.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to examine the safety of long term repeat exposure to rapastinel (GLYX-13) in subjects who participated in GLYX13-C-202.

The primary endpoint of this study is to examine the number of participants who experience an adverse event over the course of the study.

[redacted]

6 STUDY DESIGN

6.1 Overall Study Design

This is a phase 2 open label safety study of GLYX-13 for participants who completed 12 weeks of treatment in GLYX13-C-202 (NCT01684163).

At the screening visit, the Structured Clinical Interview for Depression (SCID) will be administered to determine whether any exclusionary conditions have arisen since subject's completion of GLYX13-C-202. [redacted]. A physical examination will be conducted to ascertain if significant changes have occurred since the subject ended participation in GLYX13-C-202. Blood and urine samples will be obtained for laboratory analysis. Antidepressant agents used since the subject ended participation in GLYX13-C-202 will be recorded.

On Week 1, subjects will arrive at the investigative site having fasted for at least 10 hours, with water as desired. Each subject's eligibility will be confirmed; then a physical examination will be performed, and blood and urine samples for laboratory analysis will be obtained. Vital signs will be assessed and mass recorded. ECG will be recorded, [redacted]. Each subject will then receive an IV dose of rapastinel (GLYX-13), 225 mg or 450 mg (replaces 5 mg/kg or 10 mg/kg, respectively) in a "slow bolus" injection in an upper extremity vein within approximately 1 to 2 minutes. Subjects will be discharged following determination by the investigator that they are medically able to leave.

Subjects will return to the study site during the first month on the schedule (weekly or biweekly) to which they were assigned in GLYX13-C-202. After the first month subjects will return to the study site on a schedule defined by treatment plan set by the investigator. [redacted] Rapastinel (GLYX-13) will be administered. Subjects will remain in the study unit until determination by the investigator that they are medically able to leave the study unit.

[redacted]. ECG will be recorded and blood and urine samples will be obtained for laboratory analysis. Rapastinel (GLYX-13) will be administered. Subjects will remain in the study unit until determination by the investigator that they are medically able to leave.

6.2 Dose Level

Unit doses of rapastinel (GLYX-13), 225 mg/3 mL or 450 mg/3 mL IV, will be administered in a "slow bolus" injection to each subject in an upper extremity vein within approximately 1 to 2 minutes. Investigator will begin treatment based on the dose level (5 mg/kg or 10 mg/kg) to which the subject was assigned during participation in GLYX13-C-202; subjects originally assigned to 5 mg/kg will receive 225 mg/3 mL, and subjects originally assigned to 10 mg/kg will receive 450 mg/3 mL. If subject experiences adverse event(s) that the investigator believes may be associated with rapastinel (GLYX-13), the investigator may decrease dose level from 450 mg to 225 mg. If at any point the patient cannot tolerate the minimum 225 mg unit dose, the patient should be discontinued from the study.

6.3 Treatment Plan

Following one month at the dose level (subjects who were assigned to placebo during the randomized withdrawal phase of GLYX13-C-202 are eligible to participate and will begin at the dose level to which the subject was assigned during the stabilization phase of GLYX13-C-202) and dose interval to which the subject was assigned during the randomized withdrawal period of GLYX13-C-202, the investigator may continue the same dose level and dose interval, or may change the dose level and dose interval. The investigator will complete a treatment plan that outlines the dose level and dose interval at which rapastinel (GLYX-13) will be administered. The investigator, at the investigator's discretion, may change the treatment plan to alter dose level and/or dose interval based on the subject's depression status.

6.4 Duration of Subject Participation

Each subject will receive rapastinel (GLYX-13) until rapastinel (GLYX-13) is approved for marketing by the U.S. FDA or until the subject discontinues from the study, or until the Sponsor stops the study.

7 SELECTION OF STUDY POPULATION

7.1 Inclusion Criteria

The subject must meet the following criteria to be eligible for enrollment into this study:

1. Participants who have completed 8 or more weeks of treatment in the preceding study (GLYX13-C-202, NCT01684163

2. Participants who wish to continue treatment with rapastinel (GLYX-13) after the preceding study

3. Meets Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) criteria for major depressive disorder (MDD)

4. Female subjects of childbearing potential with a negative serum pregnancy test prior to entry into the study and who are practicing an adequate method of birth control (eg oral or parenteral contraceptives, intrauterine device, barrier, abstinence) and who do not plan to become pregnant during the course of the study. Female subjects may be included without a negative serum pregnancy test if they are surgically sterile or at least 2 years post-menopausal.

5. Clinical laboratory values <2 times the upper limit of normal (ULN) or deemed not clinically significant per the investigator and medical monitor

6. Ability to understand the requirements of the study, provide written informed consent, abide by the study restrictions, and agree to return for the required assessments

7. Based on the investigator and medical monitor's clinical judgment, subjects with eating disorders, obsessive compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), and generalized anxiety disorders secondary to major depressive episodes (MDEs) are permitted.

7.2 Exclusion Criteria

The subject will not be eligible for enrollment if any of the following criteria are met:

1. Axis I diagnosis of delirium, dementia, dysthymia, amnestic or other cognitive disorder, schizophrenia or other psychotic disorder, bipolar I or II disorder, eating disorder (anorexia or bulimia nervosa), obsessive-compulsive disorder, panic disorder, acute stress disorder, agoraphobia, social phobia, attention-deficit hyperactivity disorder (ADHD), or PTSD

2. A clinically significant current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder

3. Experiencing hallucinations, delusions, or any psychotic symptomatology in the current episode; lifetime history of psychosis

4. Huntington's, Parkinson's, Alzheimer's, Multiple Sclerosis, or a history of seizures or strokes

5. Currently hospitalized or residing in an in-patient facility during study participation

6. Substance abuse since the end of participation in GLYX13-C-202, including greater than or equal to 5 units of alcohol per day where 1 unit = ½ pint of beer, 1 glass of wine 4 oz, or 1 oz. of spirits consumed most weeks or in the opinion of the investigator

7. Women who are planning to become pregnant during the course of the study

8. Allergy or intolerance to current antidepressant or other current medications

9. Participation in any clinical trial of an investigational product or device within 30 days of enrollment in this trial with the exception of GLYX13-C-202.

10. Positive screen for drugs of abuse: cocaine, marijuana, PCP, ketamine, opioid or other agent that in the opinion of the investigator is being abused

11. Pose current (past 6 months) suicide risk based on administration of the C SSRS and the investigator's clinical judgment

12. Human immunodeficiency virus (HIV) infection (based on the based on the HIV-1 & HIV-2 antibody screen) or other ongoing infectious disease

7.2.1 Adequate methods of birth control

Over the course of the study, females of childbearing potential must practice a method of contraception with greater than 90% reliability. Women of childbearing potential are women who are not 2 years postmenopausal, or not surgically sterile. Typical acceptable forms of birth control are:

- cervical cap with spermicide
- diaphragm with spermicide
- male condom
- oral contraceptives
- intrauterine devices
- medroxyprogesterone acetate
- levonorgestrel subdermal implants
- abstinence

7.2.2 Permitted Concomitant Treatment

Subjects may use any drug not specifically excluded in the exclusion criteria.

During the study, subjects will be reminded to abstain from alcohol and not to use illegal drugs or prescription drugs not prescribed by a doctor.

Cough syrup with dextromethorphan cannot be used within 2 weeks before the baseline visit and cannot be used during the study.

7.2.3 Recording of Prior/Concomitant Therapy

All antidepressant drugs and other drugs taken during the current depressive episode to within 30 days of Screening will be carefully documented. During the study, subjects will report permitted concomitant drugs taken to the site study personnel during each study visit.

8 STUDY DRUGS

Rapastinel (GLYX-13) 450 mg IV Prefilled Syringes: [redacted]

Rapastinel (GLYX-13) 225 mg IV Prefilled Syringes: [redacted] .

8.1 Study Drug Storage Conditions

Study drug must be stored refrigerated [redacted]

Drug supplies will be kept in an appropriate secure area and stored in accordance with specifications on the drug labels. Site will maintain shipment records from the depot and ensure supplies are received under the proper conditions. A drug inventory record of supplied, received, dispensed, and returned study drug must be maintained by the pharmacy representative on an ongoing basis. The investigator is required to return unopened kits of study drug to the Sponsor at the end of the trial (Sponsor will provide specific instructions). The pharmacy representative is required to maintain copies of study drug shipping receipts, drug accountability records, and records of return or final disposal of study drug. This form must be available at all times for inspection by the medical monitor or field monitor.

8.2 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned initially to the dose level and frequency to which they were assigned during the randomized withdrawal portion of clinical study GLYX13-C-202. Following one month of participation, dose level and dose frequency may be changed by the investigator according to a treatment plan formulated by the investigator at the investigator's discretion.

8.3 Study Drug Dosing

Study drug will only be administered to eligible subjects under the supervision of the investigator or identified subinvestigator(s) or other assigned personnel licensed to administer IV drugs.

Table 2 Dose Volumes for Dosing

Dose Level mg IV	Dose Volume (mL/subject)	This replaces
225	3.0	5 mg/kg
450	3.0	10 mg/kg

Study drug (rapastinel [GLYX-13]) will be administered using a syringe attached to a butterfly catheter in a "slow bolus" to an upper extremity vein to each study subject within approximately 1 to 2 minutes.

8.3.1 Blinding

This is an open label safety study.

8.4 Dose Interval

Dose interval for the first month of participation will be that (weekly or biweekly) to which the subject was assigned during the randomized withdrawal phase of GLYX13-C-202. The investigator will then formulate a treatment plan in which dose interval will remain the same or change. The treatment plan may be modified from time to time by the investigator if it is deemed prudent based on subject's depression status.

8.5 Receipt of Supplies

Upon receipt of the investigational drug, the pharmacist or designee will visually inspect the shipment and verify the drug information, quantity, and condition of the study drug received. The pharmacist will complete the accompanying Temptale form by following the instructions on the form.

The study drug will be supplied in kits, each containing 1 prefilled syringe, a plunger, and a needle, and labeled with the protocol number, kit number, contents, lot number, storage information, Sponsor, warning language ("Caution: New Drug—Limited by Federal Law to Investigational Use. Keep Out of Reach of Children"), and instructions for use to refer to protocol, as well as fields for the patient identification (PID) number, patient initials, study center number, visit number, and date dispensed to be recorded. The study center will write on both panels the patient's PID number and patient's initials along with the study center number, visit number, and date dispensed.

The study center personnel will complete the kit label and attach the tear-off portion to the source documents.

The prefilled syringe will be labeled with the protocol number and kit number. The study center personnel will write the PID number on the prefilled syringe associated with the kit mentioned above. The prefilled syringe will not have a tear off and will remain on the prefilled syringe. .

8.6 Study Drug Accountability

The Sponsor will provide the investigator with sufficient amounts of the study drug to begin the study. It is the responsibility of the investigator to ensure that a current record of inventory/study drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor during the study and are open to inspection by regulatory authorities at any time.

Pharmacy personnel or other designated site staff will account for, store and dispense the study drug. At the end of the study, all study drug must be accounted for. In addition, at the end of the study, all unused study drug should be returned to the Sponsor or the local distributor at the address provided in the SSARF (Study Specific Accountability Return Form).

8.7 Study Drug Handling and Return

The study drug must be stored refrigerated [redacted]. Sites must report any temperature excursions as described in the Study Reference Manual or contact the Sponsor or its designee for further instructions.

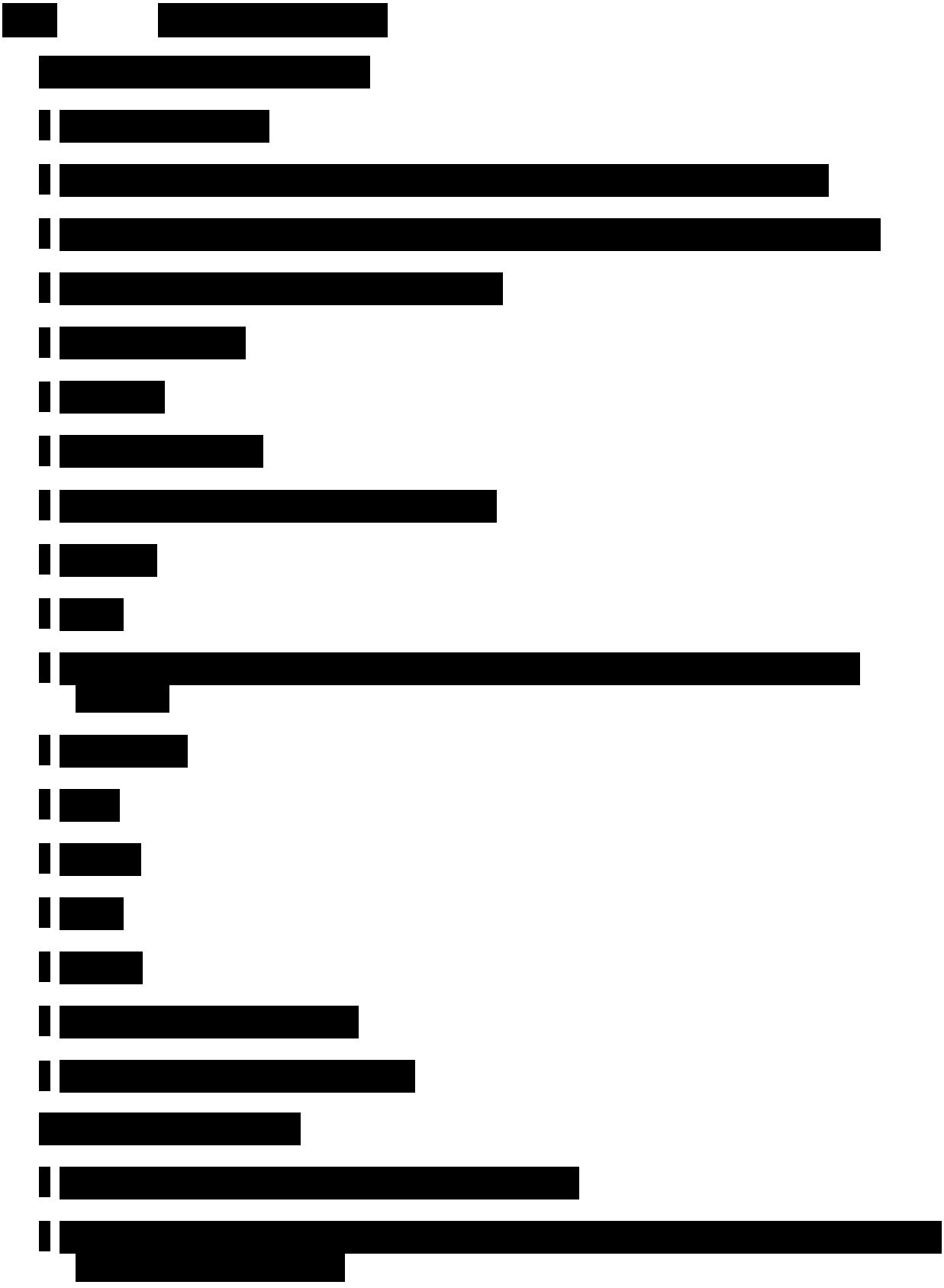
Upon completion or termination of the study, all unused kits of study drug will be returned to the Sponsor's representative. The site will dispose of any used study drug as part of the site internal SOP for disposing of sharps and biohazard material. Instructions for return of unused study drug will be supplied near completion of the study.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Standardization of Data Capture

Dosing of study drug to subjects in this study will be performed by a qualified designee under the supervision of a licensed health care provider listed on the FDA Form 1572. Accurate, consistent, and reliable data will be ensured by using standard practices and procedures presented by the sponsor and applicable regulatory authorities.

[redacted]



[redacted]

9.2.7 Total Blood Collection Volume

The total volume of blood collected over each year of participation will be less than 100 mL.

10 SUBJECT AND STUDY DISCONTINUATION

10.1 Screen Failures

Subjects who sign and date the informed consent form (ICF) but who fail to meet the inclusion and exclusion criteria are considered screen failures. A screening log, which documents the subject initials and reason(s) for screen failure, is to be maintained by the investigator for all screen failures. A copy of the log should be retained in the investigator's study files. Subjects may be rescreened on a case-by-case basis upon discussion between the investigator and the Medical Monitor.

10.2 Discontinuation from Study

A subject may be prematurely discontinued from the study for any of the following reasons:

- Adverse event
- Withdrew consent
- Physician decision
- Pregnancy
- Protocol deviation
- Lost to follow-up
- Site terminated by Sponsor
- Study terminated by Sponsor
- Other

10.3 Site Discontinuation

Reasons for discontinuation of the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Investigator request to withdraw from participation.
- Sponsor decision.
- Serious and/or persistent non-compliance by the investigator with the protocol, the clinical research agreement, the Form FDA 1572 or applicable regulatory guidelines in conducting the study.
- Institutional review board (IRB) decision to terminate or suspend approval for the investigation or the investigator.
- Investigator fraud (altered data, omitted data, or manufactured data).

11 EFFICACY ASSESSMENTS

[redacted]

[redacted]

12 SAFETY ASSESSMENTS

[redacted]

12.7 Adverse Events

Subjects should be queried in a non-leading manner, without specific prompting (eg, "How are you feeling?"). The site study staff should assess emerging symptoms of dissociative reaction similar to those caused by other NMDA antagonists including memory impairment, disturbance in time, body or environmental perception, stilted speech, emotional withdrawal, impaired coordination, motor retardation, bizarre reasoning or illusory experiences in any sensory perception, or confused state; such symptoms may be captured as adverse events.

An "adverse event" is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with an investigational product, regardless of causal relationship. A "pre-existing" condition is one that is present before study drug dosing and is reported as part of the subject's medical history. Pre-existing conditions should be reported as an AE only if the frequency, intensity, or character of the pre-existing condition worsens during the course of the study.

Laboratory abnormalities are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. However, a laboratory abnormality (eg, a clinically significant change detected on clinical chemistry, coagulation, hematology, urinalysis) that is independent from the underlying medical condition and that requires medical or surgical intervention, or leads to study drug interruption or discontinuation, must be considered an AE.

12.7.1 Recording of Adverse Events

Subjects should be instructed to report all AEs to the investigator. AE collection begins at signing of ICF and ends 30 days after last dosing injection. In addition, the investigator should seek to elicit any clinical or objective reactions by specific questioning (eg, "How have you been feeling?") and, as appropriate, by examination. Information on all AEs should be recorded on the eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. The component parts of the diagnosis may be listed for verification. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality.

To avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology on the eCRF and on the medical record rather than in the subject's own words. Each AE will also be described in terms of duration (start and stop date), severity, association with the study drug, action(s) taken, and outcome.

12.7.2 Severity of Adverse Events

All AEs will be assessed for severity, using the following general grading scale:

GRADE 1 Mild: Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.

GRADE 2 Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.

GRADE 4 Life-threatening: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Severity grades for specific safety parameters will be assigned according to the National Institute of Allergy and Infectious Diseases, DMID Adult Toxicity Table (Modified) in Appendix I. For AEs involving a body system or laboratory value not included in the DMID table, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 (2009) will be used. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

12.7.3 Relationship Assessment

For each reported AE, the investigator must assess the relationship of the event to the study drug using the following scale:

Unrelated

- Does not follow a known response pattern to the suspect study drug (if response pattern is previously known).
- Can clearly be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Unlikely Related

- The temporal sequence from dosing of the study drug suggests that a relationship is unlikely.
- Follows a response pattern that is unlike that of the suspect study drug (if response pattern is previously known).
- Could be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Possibly Related

- Follows a reasonable temporal sequence from dosing of the study drug.
- May follow a known response pattern to the suspect study drug (if response pattern is previously known).
- Could also be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Probably Related

- Follows a reasonable temporal sequence from dosing of the study drug.
- Could not be reasonably explained by the known characteristics of the subject's clinical state or any other modes of therapy administered to the subject.
- Is confirmed by improvement on stopping or slowing dosing of the study drug, if applicable.

When an assessment is not provided, the event will be treated as Possibly Related for purposes of regulatory reporting.

12.7.4 Action Taken

For each reported AE, the investigator must document the action taken according to the following criteria:

- No action taken
- Non-pharmacologic treatment added
- New drug therapy added
- Discontinued from study
- New or prolonged hospitalization

12.7.5 Outcome

For each reported AE, the investigator must document the outcome according to the following criteria:

- Recovered
- Ongoing
- Unknown
- Death

12.8 Serious Adverse Events

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

- Death

  "Death" is an outcome and is NOT the AE. In the event of death, the cause of death should be recorded as the AE. The only exception is "sudden death" when the cause is unknown.

- Is a life-threatening experience

  Life-threatening AEs include any adverse drug experience, which, in the view of the investigator, places the subject at immediate risk of death from the reaction as it

occurs. It does not include a reaction that, had it occurred in a more serious form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity

  Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

- Results in a congenital anomaly/ birth defect
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Example: allergic bronchospasm requiring intensive treatment in an emergency room or at home.

All SAEs that result in death or are life-threatening, regardless of causal relationship, must be reported to the medical monitor within 24 hours of the site's knowledge of the event. A copy of the initial SAE report must be received within one (1) business day.

All other SAEs or other events reportable to FDA and/or IRB will be forwarded to the medical monitor within one (1) business day.

The SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: subject identification, reporting source, and an event outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor will contact the investigational site to solicit additional information or to follow up on the event.

If there is any doubt whether the information constitutes an SAE, the information will be treated as an SAE for the purposes of this protocol. Serious adverse event collection will begin after signing the ICF and end 30 days after the last dose.

Serious adverse events will be followed until resolution or return to baseline (when worsening of a pre-existing condition is reported).

All relevant documentation pertaining to the SAE (additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) will be provided by the investigator to the medical monitor in a timely manner.

[redacted]

[redacted]

13 DATA MANAGEMENT

Study data will be entered into eCRFs. Before data analysis, programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data. All issues resulting from the computer-generated checks will be resolved.

14 STATISTICS

14.1 General Considerations

Quantitative assessments will be summarized using descriptive statistics including the mean, standard deviation, median, minimum and maximum values. Changes from baseline will be summarized where appropriate.

Qualitative assessments will be reported as frequencies and percents within each assessment level. Unless specified otherwise, the denominator for percents will the number of subjects in each treatment group. Shift tables may be produced for some assessments and will contain counts of subjects in each cross-classification level of baseline versus post-baseline assessment without percents. Only subjects with a baseline will be included in these tables but a missing category will be permitted for post-baseline values.

The baseline value for a given assessment will be the last non-missing observation collected before administration of study drug.

14.2 Study Populations

Subject disposition, demographics, and baseline assessments will be summarized using all enrolled subjects, whether or not the study drug was received.

The safety population will consist of all subjects who received any injection of study drug. All safety summaries will be based on this population.

The full analysis set (FAS) will consist of all subjects who received any injection of study drug and who have at least one post-baseline efficacy assessment. All efficacy summaries and analyses will be produced using this population and it will be considered the primary efficacy population.

[redacted]

14.4 Sample Size Determination

This study is open to subjects who participated in clinical study GLYX13-C-202 at specified investigative sites. Up to 100 subjects are eligible.

[redacted]

14.6 Pharmacokinetic Analysis

No pharmacokinetics samples will be obtained during this study.

15 ADMINISTRATIVE ASPECTS

15.1 Compliance with Regulatory Requirements

This protocol will be conducted in compliance with the protocol and all regulatory requirements, in accordance with Good Clinical Practices (GCP), including International Conference on Harmonization (ICH) Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

15.2 Institutional Review Board Approval

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB for approval. IRB approval of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The principal investigator is responsible for keeping the IRB advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The principal investigator is also responsible for notifying the IRB of any significant AEs that occur during the study.

The Sponsor will submit all protocol related documents for approval by the IRB for those sites able to use a central IRB.

15.3 Informed Consent

It is the policy of the Sponsor that written informed consent is obtained from subjects. The informed consent document must be signed and dated before the initiation of non-routine study-related tests, and before dosing of study drug. The original signed ICF for each participating subject shall be filed with records kept by the investigators(s). A copy of the informed consent document must be provided to the subject. If applicable, it will be provided in a certified translation of the local language. HIPAA requirements will be included in the ICF.

The subject's Bill of Rights will be included in the Informed Consent process in sites located in California.

15.4 Confidentiality

Personal study subject 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 the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor, the IRB approving this research, and applicable regulatory authorities 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 presentation of the results of this study at meetings or in publications, the subjects' identity will remain confidential.

15.5 Compensation, Insurance and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

15.6 Protocol Amendment

If a protocol has been filed with regulatory agencies or submitted to an IRB and requires changes, a protocol amendment must be written. Any changes to the protocol will be made by the sponsor. All amendments will be sent to the IRB on the study sites' behalf. Sites using a local IRB are then responsible for submitting the amendment to their local IRB for approval.

15.7 Case Report Forms

An electronic CRF (eCRF) will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel within 72 hours of the study visit. The eCRF will be signed by the principal investigator or a subinvestigator listed on the FDA Form 1572. It is the responsibility of the principal investigator to ensure the CRFs are completed and submitted to the Sponsor (or designee) in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change and person making change).

15.8 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondences, computer printouts, laboratory data, and drug accountability records. All source documents produced in this study will be maintained by the Investigator(s) and made available for inspection by Sponsor representatives, the FDA and any other applicable regulatory authorities.

15.9 Study Monitoring Requirements

Site visits will be conducted by an authorized Sponsor representative (the monitor) to inspect study data, subject's medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective US or national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRFs.

The Investigator will permit staff and contracted representatives of the Sponsor, the FDA, and/or respective health authorities to inspect facilities and records relevant to this study.

15.10 Study File Management

It will be the responsibility of the investigator(s) to assure that the study file at the site is maintained. The study file will contain, but will not be limited to, source documents, CRFs, and all other administrative documents, eg, IRB correspondence, clinical trial materials and supplies shipment manifests, monitoring logs, Sponsor correspondence, and so forth. A study-specific binder will be provided with instructions for the maintenance of study records.

15.11 Study Completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated: source documents, completed, and signed CRFs.

15.12 Audits

During the course of the study, or after completion of the study, each study site may be subject to an audit by a Quality Assurance Auditor (or an auditor appointed by the Sponsor or its authorized representative) and/or an inspector from the FDA and/or other regulatory authority. Every attempt will be made to notify the Investigator in writing in advance of the audit.

15.13 Retention of Records

According to US Investigational New Drug (IND) regulations (21 CFR 312.62), records and documents pertaining to the conduct of this study and the distribution of study drugs including CRFs, ICFs, laboratory test results, and drug inventory records will be retained. These records will be kept on file by the principal investigator for 2 years after a marketing application is approved for the drug for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified. Per ICH guidelines, documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the investigator when records and documents no longer need to be retained. No study records should be destroyed without prior written authorization from the Sponsor.

15.14 Disclosure of Data

The investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of investigators, their addresses, qualifications and extent of involvement. It is understood that the Investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the FDA and other regulatory authorities, by the Sponsor, and the IRB as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel

responsible for his or her welfare. Subject medical information obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

15.15 Financial Disclosure

The FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require sponsors to obtain certain financial information from investigators participating in covered clinical studies; each principal investigator and subinvestigator is required to provide the required financial information and to promptly update the Sponsor with any relevant changes to their financial information throughout the course of the clinical study and for up to 1 year after its completion. This rule applies to all investigator(s) and subinvestigator(s) participating in covered clinical studies to be submitted to the FDA in support of an application for market approval.

15.16 Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

16 REFERENCES

1. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63:856-864.

2. Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol 2008; 28:631-637.

3. Moskal JR, Kuo AG, Weiss C, Wood PL, O'Connor S, Hanson A, Kelso S, Harris RB, Disterhoft JF. 2005. Neuropharmacology 49: 1077-1087.

4. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56-62.

5. Guy W. editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville MD, U.S. Department of Health, Education, and Welfare.

6. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. (2007). Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. American Journal of Psychiatry 2007, 164(7): 1035-1043.

7. Moskal JR, Burch RM, Burgdorf JS, Kroes RA, Stanton PK, Disterhoft JF, Leander JD. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant side effects without the psychotomimetic side effects of NMDA receptor antagonists. Expert Opin Investig Drugs 23: 243-254.

17 APPENDICES