STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Assessing the Safety, Tolerability and Long-term Efficacy of Bryostatin in the Treatment of Moderately Severe Alzheimer's Disease Subjects Not Receiving Memantine Treatment

Protocol Number:	NTRP-101-204
Date:	September 7, 2022
Study Drug:	Bryostatin 1; matching Placebo
Investigational new Drug Application (IND) Number:	71,276
Version:	6.0
Planned FPI to LPLV	Aug 2020 to Dec 2022
Study Sponsor:	Synaptogenix, Inc. (formerly Neurotrope)

Regulatory Statement

This study will be performed in compliance with the protocol and in accordance with Good Clinical Practice (GCP) (International Conference on Harmonization [ICH], Guidance E6, 1996), principles of human subject protection, and applicable country-specific regulatory requirements.

Confidentiality Statement

SPONSOR'S SIGNATURE PAGE

Title:

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Assessing Safety, Tolerability and Long-term Efficacy of Bryostatin in the Treatment of Moderately Severe Alzheimer's Disease Subjects Not Receiving Memantine Treatment

Protocol Number: NTRP-101-204

Version 6.0, September 7, 2022

Sponsor's Authorized Representatives:

Alan J Tuchman, MD

Signature

Chief Medical Officer
Synaptogenix, Inc.

Date Sept 12, 2022

Daniel J. Alkon, MD

Signature

President and Chief
Scientific Officer
Synaptogenix, Inc

Date
Sept. 8, 2022

Miao-Kun Sun, PhD

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Director of Pharmacology
Synaptogenix, Inc.

Date Sept. 7, 2022

PRINCIPAL INVESTIGATOR'S (PI) SIGNATURE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Assessing the Safety, Tolerability and Long-term Efficacy of Bryostatin in the Treatment of Moderately Severe Alzheimer's Disease Subjects Not Receiving Memantine Treatment

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Investigational Medicinal Product: Bryostatin 1

PI'S STATEMENT OF APPROVAL

Confidentiality of all information received or developed in connection with this protocol will be maintained by me, as well as all other personnel involved in the study who are employed by me. By signing this protocol, I confirm that I have read and agree to conduct the study as outlined in the protocol and in compliance with Good Clinical Practice, the Declaration of Helsinki as amended and all other applicable regulatory requirements.

Printed name of PI: _____

_____ _____

Signature Date

STUDY CONTACT INFORMATION

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PROTOCOL SYNOPSIS

Name of Company: Synaptogenix, Inc.	**Name of Study Medication: Bryostatin 1**	**Name of Active Ingredient: Bryostatin 1**

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Confirmatory Phase 2 Study Assessing the Safety, Tolerability and Long-term Efficacy of Bryostatin in the Treatment of Moderately Severe Alzheimer's Disease Subjects Not Receiving Memantine Treatment

Study center(s): Approximately 20 sites in United States (US)

Protocol Number: NTRP-101-204

Study Duration: Approximately 2 years	**Study Phase:** 2

Objective:

Primary objective:
To evaluate the safety, tolerability, and long-term efficacy of bryostatin 1 (hereafter referred to as bryostatin) for the treatment of moderately severe Alzheimer's disease (AD).

Study Drug: Bryostatin 1 or matching Placebo

Route of Administration: Intravenous by continuous infusion over 45±5 minutes

Number of Subjects: Approximately 100 subjects (approximately 220 subjects screened)

Study Design

This is a randomized double-blind placebo-controlled, Phase 2 study comparing bryostatin-1 to placebo for long-term efficacy in the treatment of moderately severe AD (Mini Mental State Examination, 2nd edition scores of 10-18 at baseline) in the absence of memantine. Eligible subjects will receive 7 doses of bryostatin (i.v., 20µg) or matching placebo during the first 12 weeks. A second course of treatment consisting of 7 doses will begin 30 days after the final dose of the first treatment period. Cognitive tests will be assessed at intervals during the study and 30 days after the final dose of study drug. The primary endpoint is the total SIB score assessment obtained at Week 28, following completion of 2 courses of treatment.

Randomization and Treatment

Eligible subjects will be stratified based on baseline SIB total scores and will be randomized 1:1 to one of two treatment arms: 20µg bryostatin or placebo for twelve weeks, the first treatment period. The first two doses of study drug will be a loading dose 20% higher (i.e., 24µg) than the assigned dose and will be administered one week apart. Thereafter, the assigned dose of 20µg will commence with the third dose and be administered every other week. The second course of treatment will be identical to the first, beginning 30 days after

Name of Company: Synaptogenix, Inc.	Name of Study Medication: Bryostatin 1	Name of Active Ingredient: Bryostatin 1

completion of the first course. Drug is administered IV by continuous infusion over 45(±5) minutes. Subjects are scheduled to receive seven doses over 12 weeks during the first treatment period and seven doses over 12 weeks during the second treatment period. The same treatment assigned at randomization will be administered during the second treatment period.

Cognitive Assessments

- Severe Impairment Battery (SIB)
- Mini Mental State Examination, 2nd edition (MMSE-2)
- Alzheimer's Disease Cooperative Study – Activities of Daily Living - Severe Impairment Version (ADCL-ADL-Sev)
- Neuropsychiatric Inventory (NPI) metrics.

Safety Assessments

- Treatment emergent adverse events (AEs) and Serious Adverse Events (SAEs)
- Vital signs, physical examination including body weight
- ECG parameters
- Columbia Suicide Severity Rating Scale (C-SSRS), and
- Clinical laboratory assessments (hematology, blood chemistry)

Primary Efficacy Endpoint

The primary efficacy endpoint is the change from the pre-treatment baseline in the Severe Impairment Battery (SIB) total score at Week 28, after two 12-week courses of treatment.

Secondary Efficacy Endpoints

- SIB total score at the end of the Week 42 follow-up visit, for subjects who completed week 42
- SIB total score from baseline at Week 13
- SIB total scores from baseline at Weeks 9, 20, 24 and 30
- SIB total scores from baseline at Weeks 9, 20, 24 and 30 for subjects with baseline MMSE-2 scores of 10-14 and 15-18
- SIB trends over time; individual-specific slopes of total SIB scores will be obtained for all patients.

Name of Company: Synaptogenix, Inc.	Name of Study Medication: Bryostatin 1	Name of Active Ingredient: Bryostatin 1

Exploratory Efficacy Endpoints

- Change from baseline in ADCS-ADL-Sev total score at Week 13 and Week 42, for subjects who completed week 42
- Change from baseline in MMSE-2 total score at Week 13 and Week 42, for subjects who completed week 42
- Change from baseline in NPI total score at Week 13 and Week 42, for subjects who completed week 42
-

Statistical Considerations:

The primary objective for efficacy is to evaluate whether bryostatin is better than the control with respect to the primary and secondary SIB endpoints.
Efficacy analyses will be conducted for the full analysis set (FAS), consistent with the modified intention-to-treat principle, defined as all randomized subjects who received at least one dose of randomized study medication and who had at least one post-baseline efficacy assessment.
The per protocol analysis set (PP) is defined as all patients completing the study without major protocol deviations. To be included, subjects must have received at least 11 of the14 doses (80%). The completer analysis set (CAS) will be defined as all randomized subjects who completed two 12-week courses of treatment, and who have a Week 28 SIB assessment. Efficacy analyses will also be conducted for the PP and CAS sets.

Adverse event and other safety data will be analyzed descriptively in all subjects who received any dose of study drug (including partial infusions). These data will be summarized by treatment group and by time in study.

Eligibility Criteria:

Inclusion

1. Written informed consent from caregiver and subject (if possible) or legally acceptable representative if different from caregiver
2. Male and female subjects 55-85 years of age inclusive
3. Cognitive deficit present for at least 2 years that meet the diagnostic criteria for probable Alzheimer's dementia.[1] The diagnosis must be confirmed at the time of the screening visit
4. MMSE-2 score of 10-18 inclusive (applies to Screening Visit only)
5. Patients must have a baseline SIB total score of at least 60 and may not have a SIB score >93 at screening
6. Neuroimaging computerized tomography (CT) or Magnetic Resonance Imaging (MRI) within the last 24 months consistent with a diagnosis of probable AD without any other clinically significant co-morbid pathologies. If there has been a significant change in the subject's clinical status since the last imaging study that is not consistent with progression of the subject's AD, an imaging study should be performed to confirm eligibility
7. Reliable caregiver(s) or informant(s) who attends the subject at least an average of 3 hours or more per day for 3 or more days per week and who will agree to accompany the subject to the clinic visits and reliably complete the caregiver questions
8. Adequate vision and motor function to comply with testing
9. If taking an approved cholinesterase inhibitor for treatment of Alzheimer's disease, must be on a stable dose for at least 3 months prior to entry into study and the dose must not change during the study unless a change is required due to an adverse effect of the prescribed medication or a clinically significant change in the patient's status
10. Subjects who are memantine naïve or have been off memantine for at least 90 days prior to initial treatment with study drug
11. Subjects on neuroleptic medications must be on a stable dose for ≥4 weeks at screening (dose adjustments will be permitted if medically necessary at the discretion of the PI)
12. Females participating in the study must meet one the following criteria:
    a. Surgically sterilized (e.g., hysterectomy, bilateral oophorectomy or tubal ligation) for at least 6 months or postmenopausal (postmenopausal females must have no menstrual bleeding for at least 1 year) or
    b. If not postmenopausal, agree to use a double method of contraception, one of which is a barrier method (e.g., intrauterine device plus condom, spermicidal gel plus condom) 30 days prior to dosing until 30 days after last dose and have

negative human chorionic gonadotropin (β-hCG) test for pregnancy at screening

13. Males who have not had a vasectomy must use appropriate contraception methods (barrier or abstinence) from 30 days prior to dosing until 30 days after last dose
14. In the opinion of the PI subjects should be in reasonably good health over the last 6 months and any chronic disease should be stable

Exclusion

1. Dementia due to any condition other than AD, including vascular dementia (Rosen-Modified Hachinski Ischemic score ≥ 5)
2. Evidence of significant central nervous system (CNS) vascular disease on previous neuroimaging including but not limited to: cortical stroke, multiple infarcts, localized single infarcts in the thalamus, angular gyrus, multiple lacunar infarcts or extensive white matter injury
3. Clinically significant neurologic disease or condition other than AD, such as cerebral tumor, chronic subdural fluid collections, Huntington's Disease, Parkinson's Disease, normal pressure hydrocephalus, or any other diagnosis that could interfere with assessment of safety and efficacy
4. Evidence of clinically significant unstable cardiovascular, pulmonary, renal, hepatic, gastrointestinal, neurologic, or metabolic disease within the 6 months prior to enrollment. If there is a history of cancer the subject should be clear of cancer for at least 2 years prior to screening. More recent history of basal cell or squamous cell carcinoma and melanoma in situ (Stage 0) may be acceptable after review by the Medical Monitor.
5. Creatinine clearance (CL) of <45ml/min
6. Poorly controlled diabetes, at the discretion of the Principal Investigator
7. Concomitant treatment with NMDA receptor antagonists such as but not limited to memantine or drug combinations containing memantine, dextromethorphan (a cough suppressant), ketamine, phencyclidine (PCP), methoxetamine (MXE), nitrous oxide (N_2O) and the following synthetic opioids: penthidine, levorphanol, methadone, dextrpropoxyphene, tramadol, and ketobemidone.
8. Use of vitamin E > 400 International Units (IU) per day within 14 days prior to screening
9. Use of more than 2,600 mg/day of acetaminophen for more than 3 consecutive days within 14 days prior to screening
10. Use of gabapentin within 14 days prior to screening
11. Use of valproic acid within 14 days prior to screening
12. Use of an active Alzheimer's vaccine within 2 years prior to screening
13. Use of a monoclonal antibody for treatment of AD within 1 year prior to screening

14. Any medical or psychiatric condition that is likely to require initiation of additional medication or surgical intervention during the course of the study
15. Any screening laboratory values outside the reference ranges that are deemed clinically significant by the PI
16. Use of an investigational drug within 90 days prior to screening
17. Suicidality defined as active suicidal thoughts during the 6 months prior to screening or at Baseline [Type 4 or 5 on C-SSRS], or history of suicide attempt in previous 2 years, or at serious suicide risk in PI's judgment
18. Major psychiatric illness such as current major depression according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition[2], current or past diagnosis of bipolar disorder, schizophrenia, or any other psychiatric disorder that might interfere with the assessments of safety or efficacy at the discretion of the PI
19. Diagnosis of alcohol or drug abuse within the last 2 years
20. Abnormal laboratory tests that suggest an alternate etiology for dementia. If the patient has prior history of serum B12 abnormality, anemia with hemoglobin ≤10g/dl, thyroid function abnormality, electrolyte abnormality, or positive syphilis serology the patient should be revaluated to determine if these potential causes of dementia have been addressed. Only if these causes have been ruled out as the cause of the dementia can the patient be enrolled.
21. History of prolonged QT or prolonged QT on screening ECG (QTcB or QTcF >499 per central reader)
22. Acute or poorly controlled medical illness: blood pressure > 180 mmHg systolic or 100 mmHg diastolic; myocardial infarction within 6 months; uncompensated congestive heart failure [New York Heart Association (NYHA) Class III or IV][3]
23. Known to be seropositive for human immunodeficiency virus (HIV)
24. Known to be seropositive for Hepatitis B or C, unless successful curative treatment for Hepatitis C (e.g., Harvoni) has been received and there is documentation that there is no Hep B/C virus detected 3 months after completion of treatment
25. AST or ALT >3x upper limit of normal (ULN) and total bilirubin >2x ULN or International Normalized Ratio (INR) >1.5
26. Prior exposure to bryostatin, or known sensitivity to bryostatin or any ingredient in the study drug
27. Any other concurrent medical condition, which in the opinion of the PI makes the subject unsuitable for the clinical study

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Phelps CH. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National

Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer’s & Dementia : The Journal of the Alzheimer's Association, 7:263–9.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5 – May 27, 2013. American Psychiatric Association. Washington, D.C.

http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jspList of References

Table of Contents

LIST OFABREVIATIONS

Abbreviation	Definition
Aβ	Beta-amyloid
AD	Alzheimer's Disease
ADCS-ADL-Sev	Alzheimer's Disease Cooperative Study – Activities of Daily Living - Severe Impairment Version
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
APP	Amyloid Precursor Protein
AST	Aspartate Amino Transferase
Aβ1-42	Beta-Amyloid 1-42
ARIA	Amyloid Related Imaging Abnormalities
βAPP	Beta-amyloid Precursor Protein
β-hCG	Human chorionic gonadotropin
BDNF	Brain-derived Neurotrophic Factor
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
CAS	Completer Analysis Set
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement
CL	Clearance
CNS	Central Nervous System
CPK	Creatine phosphokinase
CRC	Cancer Research Campaign
CSF	Cerebrospinal Fluid
CT	Computerized tomography
C-SSRS	Columbia Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
DSC	Digit Symbol Coding
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMG	Electromyography

Abbreviation	Definition
ERB	Ethical Review Board
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLAIR	Fluid Attenuated Inversion Recovery
GCP	Good Clinical Practice
GEE	General Estimating Equations
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GRE	Gradient Refocused Echo
IAP	Interim Analysis Plan
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-To-Treat
IU	International Unit
IV	Intravenous
LDH	Lactate Dehydrogenase
LSM	Least-Squares Means
MAP	Mitogen Activated Protein
ΔMI-SIB	Maximal Improvement in the Total SIB Score from the Baseline
MMRM	Mixed Model for Repeated Measures
MMSE-2	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NYHA	New York Heart Association
NMDA	N-Methyl-D-Aspartate
NOAEL	No Adverse Effect Level
NPI	Neuropsychiatric Inventory

Abbreviation	Definition
PAP	Pharmacokinetic Analysis Plan
PBMCs	Peripheral Blood Mononuclear Cells
PET	Tween 80 (polysorbate 80)
PI	Principal Investigator
PK	Pharmacokinetics
PKC	Protein Kinase C
PKCε	Protein Kinase C Epsilon
PP	Per Protocol Analysis Set
PT,	Prothrombin Time
PTT,	Partial Prothrombin Time
PVC	Polyvinylchloride
QTcB	Corrected QTC – Bazett's formula
QTcF	Corrected QTC – Fridericia's formula
RBANS	Repeatable Battery of Assessments for Neuropsychological Status
SA	Safety Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIB	Severe Impairment Battery
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	Upper limit of normal
USP	United States Pharmacopeia
US	United States
WHO-DRL	World Health Organization Drug Reference List

1 INTRODUCTION

1.0 Alzheimer's disease

Alzheimer's disease is the most common cause of dementia, affecting approximately 5.3 million people in the United States (US) and 30 million people worldwide. There is a disproportionate representation of women with nearly 2/3 of the affected individuals being female. Of the 5.3 million affected Americans, 5.1 million are older than 65 (Alzheimer's Association website www.alz.org, 2015). Since aging is the single most important risk factor for development of dementia and medical advances are prolonging survival, the incidence of AD will increase. The US Census Bureau data suggest that the number of individuals living until age 100 between the years 2000 and 2020 will increase by more than 200% and the number of individuals living until age 90-95 will double.[4] By 2050 the number of individuals with Alzheimer's disease will almost triple to a projected 13.8 million. In 2013, 15.5 million family and friends provided 17.7 billion hours of unpaid care to those with Alzheimer's and other dementias – care valued at $220.2 billion (Alzheimer's Association website www.alz.org, 2015).

The currently approved treatments for AD provide modest symptomatic benefit and do not alter the disease progression. These therapies primarily consist of cholinesterase inhibitors [tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (galanthamine, Reminyl)] and the N-methyl-D-aspartate (NMDA) antagonist, memantine (Namenda). The development of a medication that produces a significant improvement in clinical symptoms and/or slows the progression of the disease would be a significant advance in the therapeutics of AD.

The protein kinase C (PKC) signaling pathways have been shown to play an integral role in learning and memory. Several animal models have demonstrated that PKC is involved in the learning process.[5, 6] In addition, PKC activity regulates phosphorylation of Tau and cleavage of Aβ amyloid through its effects on alpha secretase and GSK3β.[13] The single most important risk factor for the sporadic form of AD, increased age, has also been linked to impaired PKC-mediated α-secretase activation.[7] Aged animal models, for example, have shown age-specific changes of PKC isozyme distribution in the brain,[8, 9] impaired PKC translocation, reduced levels of the PKC anchoring protein, RACK1,[10] alterations in mitogen activated protein (MAP) kinase Erk1/2,[11] and reduced levels of the α-secretase cleaved Amyloid Precursor Protein (APP), soluble amyloid precursor protein alpha (sAPPα), in the cerebrospinal fluid (CSF).[12] Aging of normal human fibroblasts also reduced secretion of sAPPα.

The demonstration of reduced levels of PKC in the brain of Alzheimer's subjects suggests a potential target to improve cognition in AD is the activation of PKC which in turn activates a series of downstream pathways that enhance synaptic function and promote synaptogenesis. Bryostatin is a potent stimulator of PKCε and is non-tumorigenic. Hongpaisan et.al [13] have recently demonstrated the cognitive benefits and the effect on synaptogenesis in two strains of transgenic AD mice. Their work was recently reproduced by Schrott, et.al.[14] Activation of PKCε by bryostatin was associated with reduced levels of β amyloid, increased levels of the

Brain Derived Neurotropic Factor (BDNF), prevention of synapse loss, reduced plaque formation and restored memory and learning even in the presence of plaques.

1.1 Rationale for the use of bryostatin in the treatment of AD

The pharmacological basis for the use of bryostatin for the treatment of AD is based on the hypothesis that low dose, intermittent administration of bryostatin will activate PKC isozymes α and ε. Activation of PKC is associated with:

- Enhanced associative learning and recent memory via PKC-mediated phosphorylation of downstream substrates
- Increased synthesis of proteins such as MAP kinase Erk1/2, and synaptogenic proteins such as BDNF required for long-term memory
- Activation of α-secretases, thereby increasing non-toxic fragments of the beta-amyloid precursor protein (βAPP) and reducing the neurotoxic fragment of βAPP, $A\beta_{1-42}$, and the associated neuropathology
- Activation of $A\beta_{1-42}$ – degrading enzymes
- Phosphorylation of GSK-3 beta, inhibiting production of Tau and the associated neuropathology
- Improved memory and learning in 3 different strains of transgenic mice with single or multiple Alzheimer's gene mutations even in the presence of amyloid plaque [13-15]

Thus, activation of PKC can enhance existing synaptic function, reduce the toxic effects of amyloid and promote synaptogenesis, all potential targets to improve cognitive function in AD.

1.2 Pharmacokinetics, Toxicology and Drug Metabolism in Animals

Single dose toxicity of bryostatin has been characterized in four non-GLP studies conducted under National Cancer Institute's (NCI) IND, including three IV toxicity studies in mice and one IV toxicity study in rats. Bryostatin was evaluated in a single GLP–repeated dose 21-day IV toxicity study in rats. The single dose toxicity studies were conducted using two different dosing formulations: bryostatin in ethanol/saline or bryostatin in polyethylene glycol, ethanol, and Tween 80 (PET) diluent. LD_{50} ranged from a low of 38µg/kg to 75µg/kg. The 21-day repeat-dose toxic study performed in rats at doses of 0, 10, 15 and 25µg/m^2 with the ethanol/saline formulation resulted in no relevant toxicology findings. The maximum tolerated dose (MTD) and no adverse effect level (NOAEL) were noted to be 25µg/m^2 the highest dose studied. However, since there were no toxicologically relevant findings, the report suggested that the MTD and NOAEL are greater than 25µg/m^2.

Two preliminary dose range finding IV toxicology studies were performed in the rat and dog to characterize the toxicity of bryostatin and to estimate the maximum tolerable dose (MTD) when administered by bolus injection and continuous infusion. In the Sprague-Dawley rat bryostatin was tolerated up to 10µg/kg (infusion) and 15ug/kg (bolus) with no significant differences in toxicity noted between the two routes of administration. In the beagle dog bryostatin was tolerated at doses up to 15µg/kg (infusion and bolus). There were no

significant differences in toxicity between the two routes of administration. A more detailed results summary can be found in the Investigator's Brochure.

Limited pharmacokinetics (PK) data are available in animals. The pharmacokinetics of bryostatin was analyzed in female CD1/F2 mice by using [C26-3H]-labeled bryostatin following IV and IP administration (Zhang et al 1996). Following IV administration of 40µg/kg (120mg/m^2), the plasma disappearance curve for bryostatin could be described by a 2-compartment model, with a distribution $t_{½}$ of 1.05 hours and an elimination $t_{½}$ of 22.96 hours. In contrast, following IP administration, the plasma disappearance curve was better described by a first-order absorption one-compartment model, with an absorption $t_{½}$ of 0.81 hours and an elimination $t_{½}$ of 28.76 hours.

Urinary excretion represented the major pathway of elimination in the first 12 hours after IV administration, with 23.0 ± 1.9% (mean ± standard deviation) of the administered dose excreted. Approximately equal amounts of radioactivity (40%) were excreted in feces compared with urine within 72 hours after IV administration. A greater area under the curve, longer mean resident time, and lower clearance were observed with IP administration compared with IV administration. Bryostatin was widely distributed to various tissues following both IV and IP administration. However, accumulation was observed in the lung, liver, gastrointestinal (GI) tract, and fatty tissue.

1.3 Genotoxicity

Bryostatin 1 was evaluated using the bacterial reverse mutation assay (i.e., the Ames test) with no positive responses observed. Bryostatin 1 was evaluated as negative (nonclastogenic) in the micronucleus assay; it was also evaluated as negative (non-DNA damaging) in the Comet Assay. Overall, based on the results of the Ames test and the combined micronucleus/comet assay, bryostatin 1 is not considered to be genotoxic.

2 CLINICAL TRIAL DATA

2.0 Oncology Data

Safety data are available from published clinical studies of bryostatin for the treatment of cancer. Altogether, over 1400 oncology subjects received bryostatin, mainly under NCI's IND # 42,780, with exposures to bryostatin in both single and combination agent studies. About 584 subjects received bryostatin as monotherapy, with dose levels ranging from 5µg/m^2 to >180µg/m^2. Most subjects in both the monotherapy and combination therapy studies received bryostatin at doses >25µg/m^2, most often as 1-hour infusions administered at various time intervals from weekly infusion to continuous infusions for 72 hours. Most studies were repeated dose studies where subjects received treatment for several weeks (See Investigators Brochure).

Adverse events occurring in the single agent studies that resulted in discontinuation from the studies were myalgia (28 subjects), acute transient reaction (dyspnea, flushing, hypotension, and bradycardia; 4 subjects each), phlebitis (attributed to ethanol in the formulations, 6 subjects), fatigue (3 subjects), and 1 subject each with bacteremia, chest pain, dehydration,

dysphagia, hematuria, nausea, skin rash, subclavian vein thrombosis, thrombocytopenia, and vomiting. The following AEs were associated with death in the single agent trials: cardiac arrest (2), hypotensive with evidence of renal and hepatic failure (1), perforated gastric ulcer (1), renal function decline with cardiac arrest and perforated gastric ulcer (1; PIs considered not related to bryostatin), and sudden death (1; PIs considered likely to be cardiovascular event). Relatedness to bryostatin treatment was not assessed except where noted.

Other severe (Grade 3 or higher) AEs reported in the single agent clinical studies in cancer subjects included: alkaline phosphatase (ALP) (elevated; subject had pre-existing liver metastases), allergic reaction, anemia, anorexia, arthralgia, ataxia, cardiac arrhythmias, cardiovascular, coagulation, community-acquired pneumonia, congestive heart failure, constipation, dermatitis, dermatologic, diarrhea, dyspnea, edema/weight gain, fever, gastrointestinal, genitourinary, granulocytopenia, headache, hepatic, hyperbilirubinemia, hyperglycemia, hypokalemia, hyponatremia, infection, leg weakness, lymphedema, lymphocytopenia, myocardial infarction, neurotoxicity, neutropenia, pain (abdominal, back, eye, site not specified), pulmonary, pulmonary embolus from inferior vena cava tumor thrombus, sepsis and pneumonia without neutropenia, syncope, and urinary frequency.

The absence of a Placebo-control group in bryostatin oncology studies makes it difficult to determine the extent to which underlying disease or concomitant medications may have contributed to this safety profile.

2.1 Alzheimer's Disease Data

2.1.1 Study NTRP101-203

NTRP 101-203 was a randomized, double-blind, placebo-controlled, phase 2 trial assessing the safety, tolerability (primary objective) and efficacy (secondary objective) of bryostatin in the treatment of moderately severe to severe Alzheimer's disease subjects. This study was intended to confirm the results of study NTRP101-202 both in safety and efficacy for subjects not receiving concurrent memantine treatment at time points through Week 15.

2.1.1.1 *Methodology*

The study was designed to have an initial telephonic prescreening, followed by an actual screening period where the eligible subjects were selected and stratified based on MMSE-2 scores: 4-9 vs. 10-15 and randomized 1:1 to either 20µg bryostatin or placebo treatment arm, and then treated for 12 weeks.
The study drug was administered via continuous intravenous (IV) infusion over 45(±5) minutes. The first two doses of study drug administered were a loading dose 20% higher (i.e., 24µg) than the assigned treatment given one week apart. Subsequently, the assigned doses of 20µg were commenced as the third dose and were delivered every other week.

The primary endpoint for this study was the change from baseline to Week 13 in the Severe Impairment Battery (SIB) total score. The changes from baseline at Weeks 5, 9, and 15 in the SIB total score, and the changes from baseline at each tested time point for subjects in each

stratification group were assessed as secondary outcome measures. Individual patient's slope over time in SIB total score were evaluated via Weeks 0, 5, 9 and 13.
Exploratory outcome measures were: change from baseline in Alzheimer's Disease Cooperative Study - Activities of Daily Living – Severe Impairment Version (ADCS-ADL-Sev) total score, change from baseline in Mini Mental State Examination, 2nd edition (MMSE-2) total score, change from baseline in the 10-point Neuropsychiatric Inventory (NPI) total score, and Clinical Global Impression of Improvement Scale (CGI-I) score.

2.1.1.2 *Demographics*

A sum total of 217 subjects signed the informed consent forms. Of these subjects, 106 subjects were screen failed. The most common cause of screen failures was subject's lacking to fulfill the inclusion /exclusion criteria for eligibility of the study. A total of 111 subjects were randomized to bryostatin (55 subjects) and placebo (56) treatment arms. Of the subjects randomized to bryostatin, 96.4% (96.4%, 53/55) received treatment. The study was completed by 87.3% subjects (87.3%, 48/55) and the remaining seven subjects (12.7%,7/55) did not complete the study primarily due to withdrawal by subject (9.1%, 5/55) followed by protocol deviation and adverse event (1.8%, 1/55 each). Of 56 subjects assigned to placebo treatment, 98.2% (98.2%, 55/56) received placebo. Of these, 85.7% (85.7, 48/56) completed the study and 14.3% (14.3%, 8/56) terminated due to either subject withdrawal (5.4%,3/56), adverse event, lost to follow up, physician's decision, death or other reasons (1.8%, 1/56 each). Approximately 56% of subjects (56.5%, 61/108) in the Safety Analysis Set were females. The majority of the subjects were white (84.3%, 91/108) and not of Hispanic or Latino background. The mean (SD) age of the subjects in the Safety Analysis Set was 72 years.

No disparities between the study treatment groups were noted in majority of the baseline characteristics; however, there is a 5 unit difference in the baseline total score of Severe Impairment Battery (SIB), indicating subjects with a greater impairment were randomized to the bryostatin group. The mean baseline SIB score of the two randomized populations were 73.7 in bryostatin group and 78.6 for the placebo group.

2.1.1.3 *Safety*

A total of 116 treatment emergent adverse events (TEAEs) were reported for 47 subjects in the study (43.5%,47/108). In bryostatin group, 57 AEs were reported by 23 subjects (43.4%, 23/53). In the placebo group, 59 AEs were reported by 24 (43.6%, 24/55) subjects. The majority of AEs were either mild or moderate. A total of 16 related AEs were reported in 11 subjects (10.2%, 11/108). There were 7 related AEs reported for 5 subjects (9.4%, 5/53) in the bryostatin group, and 9 related AEs for 6 subjects (10.9%; 6/55) in placebo group. A total of 15 serious adverse events (SAE) were reported for 11 subjects (10.2%, 11/108) in bryostatin and placebo groups combined. One reported AE in placebo group resulted in death. A total of four AEs led to drug withdrawal in one subject (0.9%, 1/108). A sum total of 12 AEs led to interruption in drug scheduling regimen (4.6%, 5/108). 11 subjects reported 15 SAEs together in bryostatin and placebo groups. However, all of the 15 observed SAEs were considered to be 'unlikely related'

to the study treatment. There was one death reported in this study. The subject was randomized to the placebo group and the cause of death is unknown. Details regarding adverse events can be found on ClinicalTrials.gov, study identifier: NCT03560245.

2.1.1.4 *Efficacy*

The primary efficacy endpoint was defined as the change in the SIB total score from baseline to Week 13. Severe Impairment Battery (SIB) scoring is used to assess cognition in subjects with moderate and severe AD and is a useful outcome measure in advanced stages of disease. Forty questions are included with a point score range of 0-100. Lower scores indicate greater cognitive impairment. The mean baseline SIB score of the two randomized populations were 73.7 in bryostatin group and 78.6 for the placebo group. At week 13, the mean SIB score for bryostatin and placebo reached 76.0 and 80.9, respectively. An average increase of 1.3 point and 2.1 points was observed for the bryostatin and placebo groups, respectively at Week 13 and the difference between the treatment groups was not statistically significant.

2.1.1.5 *Summary*

The bryostatin treatment group showed minimal differences from the placebo treatment group in safety assessments, with an imbalance of 4.6 units in the baseline SIB scores between the bryostatin treatment group and the placebo group. The majority of AEs were either mild or moderate. There were no statistically significant bryostatin/placebo differences in efficacy assessments.

2.1.2 Study NTRP101-202

NTRP 101-202 was a randomized, double-blind, placebo-controlled, phase 2 trial assessing the safety and tolerability (primary objective) and efficacy (secondary objective) of bryostatin in the treatment of moderately severe to severe Alzheimer's disease subjects. Exploratory objectives characterize the pharmacokinetics (PK) and pharmacodynamics of bryostatin in this subject population. Seven doses of study drug were administered by a 45-minute continuous intravenous (IV) infusion over 12 weeks.

2.1.2.1 *Methodology*

Eligible subjects with moderately severe to severe AD were stratified based on Mini Mental State Exam (MMSE-2) scores 4-9 vs. 10-15 and randomized 1:1:1 to one of three treatment arms: 20µg, 40µg, or placebo for twelve weeks. Trial drug was administered IV by continuous infusion. The first two doses (24µg, 48µg) of each of the two active treatment arms were a loading dose, 20% higher than the assigned dose (20µg, 40µg), and were administered one week apart. Thereafter, the assigned dose commenced with the third dose and was administered every other week. Subjects were scheduled to receive seven doses over 12 weeks, with the primary efficacy measure being at Week 13, and a follow-up visit scheduled 30 days from the last dose of trial drug administration.

2.1.2.2 *Demographics*

A total of 264 subjects were screened in the trial. Of these, 147 subjects were randomized on a 1:1:1 basis to a treatment group. There were 50 subjects randomized to the placebo treatment group, 49 randomized to the 20µg bryostatin treatment group, and 48 randomized to the 40µg bryostatin treatment group. A total of 141 of the randomized subjects were treated with investigational product (IP) and were included in the Safety Analysis Set (SAS). A total of 135 subjects provided a post-baseline efficacy assessment and were analyzed as the Full Analysis Set (FAS). A total of 113 subjects out of 147 randomized (76.9%) performed a Week 13 evaluation of the SIB and were analyzed as the Completer Analysis Set (CAS). A total of 106 subjects in the SAS completed the trial (75.2%). A total of 35 subjects in the SAS and 29 subjects in the FAS withdrew early from the trial. The most common reason for early withdrawal was withdrawal of consent (18 subjects), followed by AE (11 subjects).

2.1.2.3 *Safety*

Overall, the 20µg bryostatin treatment group showed minimal differences from the placebo treatment group in safety assessments. The 40µg bryostatin treatment group had significantly greater AEs than the other treatment groups. There was also no clear difference in Serious Adverse events (SAEs) between the 20µg bryostatin group and placebo treatment groups, and again the 40µg bryostatin treatment group had significantly greater SAEs than the other treatment group.

Similarly, the placebo and 20µg group had similar numbers of TEAEs (28 events vs 30 events, respectively). The TEAEs observed more often in the 20µg treatment group vs placebo were infusion site reaction (8 events vs 3 events in placebo) and diarrhea (5 events vs 1 event in placebo). The 40µg treatment group was associated with more TEAEs than either the 20µg or placebo treatment groups across multiple system organ classes (SOC).

The most common treatment related TEAEs were grouped infusion reactions, diarrhea, headache, fatigue, and myalgia. Myalgia was seen in 5 subjects; 4 of those subjects were given the higher dose of bryostatin. Myalgia observed was mostly mild and managed with analgesics. There were also more treatment related TEAEs of diarrhea, headache, and fatigue in the higher dose bryostatin group. Both bryostatin treatment groups reported higher rates of infusion site TEAEs, and in particular the 40µg bryostatin treatment group reported 4 events of infusion site cellulitis. Although IV infusion-related reactions were also reported more often in the higher dose bryostatin group, none were reported following WebEx-based training on IV infusion and universal precautions, suggesting that this AE can be prevented. The higher dose bryostatin group also reported more TEAEs of seizure and fall compared to the lower dose bryostatin and placebo groups.

A total of 97 (68.8%) subjects in all treatment groups reported 287 separate TEAEs. Of these, 49 (34.8%) subjects reported 107 separate treatment-related TEAEs. There were 8 (16.7%) subjects with 20 treatment-related TEAEs in the placebo treatment group, 17 (37.0%) subjects with 30 events in the 20µg bryostatin treatment group, and 24 (51.1%) subjects with 57 events in the 40µg bryostatin treatment group. Six subjects had a TEAE that lead to trial drug discontinuation, 2 in the placebo treatment group, 1 in the 20µg bryostatin treatment group, and 3 in the 40µg bryostatin treatment group. Overall, 43 (30.5%) subjects had a TEAE that was mild in intensity, 46 (32.6%) subjects had a TEAE that was moderate in intensity, and 8 (5.7%) subjects had a TEAE that was severe in intensity.

There was 1 death in the trial, a subject in the 40µg bryostatin treatment group who suffered a severe TEAE of worsening of AD that was unrelated to the IP.
There were 12 (8.5%) subjects who had 14 treatment emergent non-fatal SAEs during the trial; 4 subjects with 4 events in the placebo treatment group, 2 subjects with 2 events in the 20µg bryostatin treatment group, and 6 subjects with 8 SAEs in the 40µg bryostatin treatment group. A total of 4 subjects in the 40µg bryostatin treatment group had 4 events that were judged as possibly or probably related to the IP: 3 events of cellulitis, and 1 event of seizure.
There were no apparent differences between treatment groups in laboratory assessments over time.
No differences were apparent between treatment groups when examining most vital signs, PEs, and ECG. However, there was a decline in weight in the bryostatin groups, which was more prominent in the higher dose group: 20µg bryostatin treatment group (mean loss of -1.65±2.77kg) and the 40µg bryostatin treatment group (-2.98±2.10kg), while there was a slight weight gain in the placebo treatment group (0.442±2.52kg). Further, 5 subjects in the 40µg bryostatin treatment group had 5 TEAEs of weight decreased, 3 of which were judged to be related to the IP. No weight related TEAEs were observed in the 20µg bryostatin dose group.
There were no differences between treatment groups on the C-SSRS as most subjects did not have suicidal thoughts during the trial, and there were no attempts at suicide by any subject during the trial.
Details regarding adverse events can be found on ClinicalTrials.gov, study identifier: NCT02431468.

2.1.2.4 *Efficacy*

Consistent with the initial hypothesis for bryostatin effects on PKCε and cognition, treatment with 20µg of bryostatin is effective in the treatment of Alzheimer's disease in a FAS and CAS. The overall weight of data shows that subjects treated with 20µg bryostatin displayed significant improvement on the SIB, ADCS-ADL-Sev, and other secondary and exploratory endpoints (one-sided at α=0.10), as outlined below.
Baseline scores on the SIB for the FAS were similar across all treatment groups. In the FAS, the treatment difference between the placebo treatment group and the 20µg bryostatin treatment group was statistically significant only at Week 5 (treatment difference 3.0[0.6, 5.3]$_{80\%CI}$ P=0.056). There were no statistically significant differences between the placebo treatment group and either the 20µg bryostatin treatment group or 40µg bryostatin treatment group at Week 9 or Week 13. Combining the bryostatin treatment groups and comparing with the placebo treatment group also did not produce a statistically significant difference at any time point.
For the CAS, pre-specified along with FAS to assess primary and secondary endpoints, mean scores on the SIB followed the same pattern seen in the FAS. Baseline scores were similar across all treatment groups. There was a statistically significant difference, however, between the placebo treatment group and the 20µg bryostatin treatment group at Week 5 (P=0.016), and the treatment difference at Week 13 was also statistically significant (P=0.070). Further, when both bryostatin treatment groups were pooled, there was a statistically significant difference between the placebo treatment group and pooled group at Week 5 (P=0.039) and a statistically significant treatment difference at Week 13 (P=0.094). There were no

statistically significant differences between the placebo treatment group and the 40µg bryostatin treatment group at any time point.

In the CAS there were significant differences in the ADCS-ADL-Sev at Week 13 between the placebo treatment group and the 20µg bryostatin treatment group (P=0.082), and between the placebo treatment group and pooled bryostatin treatment group (P=0.087). There were no statistically significant differences between treatment groups for the ADCS-ADL-Sev, MMSE-2, NPI, or CGI-I assays for any time point in the FAS.

In multiple exploratory analyses adjusting for covariates for the primary endpoint, there were additional significant differences between the placebo treatment group and bryostatin treatment groups. In an MMRM analysis of change from baseline in SIB total score, excluding all subjects from sites that recruited 2 or fewer subjects during the trial, there was a significant difference between the placebo treatment group and the 20µg bryostatin treatment group at Week 5 (P=0.068). There was a significant difference between the placebo treatment group and the 20µg bryostatin treatment group (P=0.031), and between the placebo treatment group and the pooled bryostatin treatment group in an MMRM analysis of change from baseline in SIB total score at the 30-day follow up visit (P=0.041). When an ANCOVA was performed to assess site effect on SIB, there was a significant difference between the placebo treatment group and 20µg bryostatin treatment group (P=0.032), and between the placebo treatment group and pooled bryostatin treatment groups (P=0.049) at Week 5. In an ANCOVA of change from baseline in SIB total score, with use of AChEI or memantine at baseline as an additional covariate, at Week 5 the 20µg bryostatin treatment group and pooled bryostatin treatment groups had statistically significant treatment differences from the placebo treatment group (P=0.024 and P=0.027, respectively).

In multiple exploratory analyses adjusting for covariates for secondary endpoints, there were statistically significant differences between the placebo treatment group and the 20µg bryostatin treatment group at Week 5 (P=0.062), and the placebo treatment group and pooled bryostatin treatment group at Week 5 (P=0.041) when performing an ANVOCA of change from baseline in ADCS-ADL-Sev total score for subjects with > median baseline ADCS-ADL-Sev total score. There was a statistically significant difference between the placebo and 40µg bryostatin treatment groups at Week 5 (P=0.099) in an ANCOVA of change from baseline in NPI Total score to assess site affects. When performing an ANVOCA of change from baseline in NPI total score for subjects with > median baseline NPI total score, there were statistically significant differences between the placebo treatment group and the 40µg bryostatin treatment group at Week 9 (P=0.054) and Week 13 (P-0.096).

No clear differences were apparent between treatment groups for Caregiver distress on the NPI, each NPI subscore at baseline, or on the NPI 10-item score.

The results for SIB score from the MSSE-2 Stratum 1 analysis show the 20µg bryostatin treatment group had a more positive response than any treatment group at Week 5 and Week 9 and the 40µg bryostatin treatment group had a slightly better response at Week 13. Results for SIB score in the MSSE-2 Stratum 2 analysis show the positive response varied across time point and treatment group. The placebo treatment group showed greater improvement in ADCS-ADL-Sev total score at Weeks 5 and 9 than either bryostatin treatment group in Stratum 1 or 2, and also at Week 13 in Stratum 2. At Week 13 in Stratum 1, the 20µg bryostatin treatment group showed the best response compared to placebo or the 40µg bryostatin treatment group.

There was a significant difference in the FAS between the placebo treatment group and the 20µg bryostatin treatment group (P=0.031), and between the placebo treatment group and the pooled bryostatin treatment group (P=0.041) in an MMRM analysis of change from baseline in SIB total score at the 30-day follow up visit.
Additional post-hoc analyses were performed on the TEAE by MMSE-2 baseline strata, SIB by BSA-adjusted Dose, ADCS-ADL-Sev by BSA-adjusted Dose, TEAE by BSA-adjusted Dose, SIB by memantine use, ADCS-ADL-Sev by memantine use, the NPI 10-item total score by memantine use, and administration site-specific TEAE. The SIB and ADCS-ADL-Sev scores also appeared to be affected by BSA-adjusted dose, as the lowest tertile of bryostatin dose in general had a better response to treatment than higher tertiles or placebo (these data were also not analyzed statistically). Subjects treated with bryostatin who did not take memantine at baseline had significantly better improvement in SIB score compared to the placebo group in an MMRM analyses of SIB total score in both the CAS and FAS. Both the pooled bryostatin and 20µg bryostatin treatment groups had significantly better scores than the placebo treatment group at Weeks 5, 13, and at 30-day Follow-up. Similar results (which were not statistically analyzed) were seen in the ADCS-ADL-Sev test and in the NPI 10-item score.

2.1.2.5 *Pharmacokinetics*

Mean plasma bryostatin concentrations increased approximately proportional to dose for an increase in dose between 20µg and 40µg, infused IV over 45 minutes. The median Tmax occurred at the end of the 45-min infusion.

Mean Cmax ranged from 0.563 ng/mL to 0.653 ng/mL after 20 µg and from 0.792 ng/mL to

1.34 ng/mL after 40µg. Mean T1/2 ranged from 1.33 h to 5.37 h. Mean CL was similar for both dose levels and ranged from 24.97 L/h to 28.42 L/h for Weeks 0 and 3. The mean CL on Weeks 7 and 11 was slightly lower, ranging from 13.38 L/h to 23.91 L/h.

Within a given dose level, the ranges of values for Cmax, AUClast, and AUCinf were consistent
across weeks and there was no indication of systemic accumulation of bryostatin during administration of bryostatin once every 2 weeks.

2.1.2.6 *Summary*

Bryostatin treatment was in general safe to use and well tolerated.
The 20µg bryostatin treatment group had similar numbers of TEAEs to the placebo treatment group except in injection site reactions and diarrhea. The 40µg treatment group had more TEAEs and SAEs than the 20µg or placebo treatment groups across many SOCs.
The 40µg dose of bryostatin was associated with more TEAEs. With a decrease in systemic CL especially noted with 40µg bryostatin dosing, the higher drug exposure may further explain the increased number of TEAEs. The most common treatment related TEAEs were diarrhea, headache, fatigue, and myalgia, and all were reported in greater frequency with the 40µg dose of bryostatin. Subjects given the 40µg dose of bryostatin also reported more TEAEs of seizure and fall.

The primary efficacy endpoint for the SIB and secondary efficacy endpoint for the ADCS-ADL-Sev was met in the CAS with the 20µg dose, which was statistically significantly different from placebo at Weeks 5 and 13. The 40µg dose was not statistically significant from the placebo.
SIB improvement was significant for the Week 5 FAS measurement ($p < .056$). No other primary or secondary endpoints were met in the FAS.
Multiple exploratory analyses in the FAS for covariates in the primary and secondary endpoints revealed additional significant differences, but these occurred predominantly at the Week 5 time point.

2.1.3 Study NTRP101-201

This was a randomized, double-blind, Placebo-controlled safety study of a single dose of bryostatin in subjects with mild to moderate AD (MMSE: 14-26). Subjects were randomized 2:1 to receive bryostatin 25µg/m^2 or Placebo. The primary objective was to evaluate the safety and tolerability of bryostatin by the incidence of AEs and SAEs. Secondary safety endpoints included assessment of physical examination, hematology including complete blood count (CBC) and platelet count, coagulation parameters, serum chemistries, ECG, urinalysis and vital signs.

The primary efficacy endpoint was a composite end point of change from baseline in the Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall and Repeatable Battery of Assessments for Neuropsychological Status (RBANS) figure recall at 48 hours post study drug infusion.

The study included single dose PK, and measurement of PKCε in peripheral blood mononuclear cells (PBMCs) as a potential biomarker.

2.1.3.1 Demographics

The study enrolled nine subjects, 4 male and 5 female, with a mean age of 71.8 ±7.4 years (range 62 to 82). The mean MMSE-2 at baseline was 22.5 for the three placebo subjects (range 19-24) and 22 (range 16-26) for the six bryostatin treated subjects.

2.1.3.2 Safety

Bryostatin was well tolerated. There were no deaths or SAEs reported. No subjects had an AE leading to withdrawal during the study. There were five treatment emergent adverse events occurring in three subjects: headache, dizziness, and papular rash. There were no reported episodes of myalgia, a known side effect of bryostatin. The only adverse event in the bryostatin treated group was headache, which was not considered related to study drug. All adverse events were mild and resolved without treatment. All laboratory assessments, including hematology, chemistry, coagulation, renal function and liver function as well as cardiac assessments were unremarkable after treatment and there was no clinically significant change in any vital signs.

2.1.3.3 Efficacy

There were no clinically significant differences between the mean or mean change from baseline between bryostatin and placebo in the HVLT-R or MMSE-2 assessments or any other efficacy assessment to suggest a treatment effect after a single dose of 25 μ g/m2 bryostatin. However, the possibility of an early effect on MMSE was identified even at small sample size and warranted further investigation in a more adequately powered trial. There was no difference in HVLT-R delayed recall or the RBANS delayed figure recall at 48 hours. Additional time points of assessment for these measures (day 2, day 4 and day 15) did not indicate any difference between groups. Additional endpoints included the change from baseline in Digit Symbol Coding (DSC), and MMSE-2 at various time points. There was no difference in mean values between groups for these endpoints at any time point. Both the treatment and the Placebo group showed an improvement in the MMSE-2 score most likely due to practice effects since the MMSE-2 was administered five times in 2 weeks.

In summary, there was no clinically significant difference between the mean or mean change from baseline between bryostatin and placebo in the HVLT-R or MMSE-2 assessments or any other efficacy assessments to suggest a treatment effect after a single dose of 25$\mu g/m^2$ bryostatin.

2.1.3.4 Pharmacokinetics

The pharmacokinetics of bryostatin were assessed in 6 subjects following 25 $\mu g/m^2$ bryostatin administered as a single 1-hour IV infusion. Individual bryostatin plasma concentrations were observed to increase and approach steady-state within the 1 hour infusion periods, and then rapidly decrease following the end of the infusion. The bryostatin maximum plasma concentrations occurred at the end of the IV infusions, and had a mean (±standard deviation (SD)) value of 1.09 ±0.25 ng/mL. A terminal elimination rate could not be calculated for most subjects due to sampling frequency, the rapid drug elimination, and the sensitivity limitations of the assay. Based on the observed individual bryostatin plasma concentration profiles, the elimination $t_{1/2}$ associated with the observed drug exposure was estimated to be less than 30 minutes. Total drug CL was observed to be high (~ 40 L/h), consistent across the individual administered doses, and did not appear to be related to body weight, BSA, or sex. The bryostatin pharmacokinetic parameters were observed to have low to moderate intersubject variability.

2.1.3.5 Pharmacodynamics/ PKCε

Preliminary assessment of PKCε concentration in PBMCs suggests there is an increase in the total amount of PKCε (cytosol plus membrane bound concentration) following treatment with bryostatin. Additional analysis is underway to further characterize the increase and pharmacodynamics.

2.1.3.6 Conclusions

This was the first double-blind assessment of the safety of bryostatin treatment in subjects with Alzheimer's disease. The study met its primary endpoint of safety and tolerability. Bryostatin appears safe and well tolerated in this cohort of subjects with mild to moderate

Alzheimer's disease. Except for an improvement in MMSE 3 hours after infusion, no improvement was detected in cognitive function on the efficacy measurements though the study was not powered to detect cognitive benefit. There was no evidence of an adverse effect on cognition following treatment with bryostatin.

3 STUDY OBJECTIVES AND HYPOTHESIS

3.0 Primary Objective

To evaluate the safety, tolerability and long-term efficacy of bryostatin for the treatment of moderately severe Alzheimer's disease in subjects not receiving concurrent memantine treatment, including 1) how long the therapeutic effects will last; and 2) whether a second treatment would be equally effective if the therapeutic effects of the first treatment do not last.

3.1 Hypothesis

Patients treated with bryostatin will experience a greater improvement in cognitive function as measured by the SIB from baseline to the primary efficacy endpoint after two 12 week courses of treatment, as compared to patients on placebo during the same time period. The null hypothesis will be rejected at a significance level of a two-sided $\alpha = 0.05$. The test of the null hypothesis will be a superiority test based on the treatment difference in Week 28 SIB from baseline means as assessed by general estimating equations (GEE) regression, and only an improvement in the SIB score from baseline is of clinical significance.

4 INVESTIGATIONAL PLAN

4.0 Overview of Study Design

This is a randomized double-blind placebo-controlled exploratory study assessing bryostatin for the treatment of moderately severe Alzheimer's disease in subjects not receiving memantine treatment. The first treatment period of the study is 15 weeks in duration, including safety and efficacy evaluation 30 days after the last treatment. Eligible subjects will be stratified based on SIB total scores at baseline and will be randomized 1:1 to treatment with 20µg bryostatin or placebo for two 12-week courses of treatment. The balance by treatment arms of baseline SIB total scores will be monitored in real time. Study drug is administered IV by continuous infusion. The first two doses of study drug will be a loading dose 20% higher (i.e., 24µg) than the assigned dose and will be administered one week apart. Thereafter, the assigned dose of 20µg will commence with the third dose and be administered every other week for 5 doses. The second treatment period, beginning at Week 15, will be identical to the first. Subjects are scheduled to receive seven doses over 12 weeks during the first treatment period and seven doses over 12 weeks in the second period according to the original blinded, randomized treatment assignment. Safety and efficacy assessments will be

done as indicated on the Schedule of Activities (Table 1). The primary endpoint is the total SIB score assessment obtained at Week 28, after completion of two courses of treatment.

4.1 Dose Rationale

The primary objective of treatment for cognitive disorders with bryostatin is activation of PKCε, not downregulation as was attempted for the oncology indications. Bryostatin activation of PKCε is dose dependent, where lower doses activate PKCε and increase de-novo synthesis of the enzyme, while higher doses of bryostatin downregulate PKCε.

The dosing regimen is based on the recently completed phase 2 study, NTRP101-202, in which the safety and efficacy analyses indicated a clear advantage of the 20µg dose over the 40µg dose.

The oncology data suggest that the dose-limiting side effect of myalgia is dose dependent and cumulative and likely related to the down regulation of PKCε. This was not seen in the NTRP101-201 study, in which there were no reports of myalgia after a single 25µg/m^2 dose of bryostatin was administered, nor in the recently completed NTRP101-202 study, in which myalgia was considered an adverse event of special interest. In NTRP101-202, in which subjects received 7 doses of study drug, myalgia was seen in 5 subjects; 4 of those subjects were given the higher 40µg dose of bryostatin. Myalgia observed was mostly mild and managed with analgesics.

Dosing in this study will begin with two initial loading doses at one-week intervals that are 20% higher than the maintenance dose (i.e., 24µg) to assure enzyme activation. Dosing will then continue with 20µg administered every other week for 5 weeks, for a total of 7 doses. The first treatment period will occur over 15 weeks, including a follow-up visit 30 days after the last dose. The same treatment regimen will be administered for subjects who qualify for a second course of treatment. The total study drug administered to a particular subject is 14 doses.

4.2 Risk/Benefit

Bryostatin treatment in study NTRP101-202 was shown to be generally safe and well tolerated. The 20µg bryostatin treatment group had similar numbers of TEAEs to the placebo treatment group except in injection site reactions and diarrhea. *Post hoc* analysis in NTRP101-202 clearly showed that bryostatin-treated subjects who did not take memantine at baseline had significantly better improvement in SIB score compared to the placebo group in an MMRM analyses of SIB total score in both the CAS and FAS. Both the pooled bryostatin (20µg and 40µg) and 20µg bryostatin treatment groups had significantly better scores than the placebo treatment group at Weeks 5, 13, and at 30-day Follow-up. There were no statistical differences in SIB score between treatment groups in subjects given memantine at baseline.

Therapeutic antibodies targeting β-amyloid have been associated with the occurrence of amyloid related imaging abnormalities (ARIA), which is similar in appearance to cerebral

vasogenic edema and microhemorrhage. A minority of cases have been associated with symptoms of headache, visual disturbance, loss of coordination, or disorientation. Asymptomatic ARIA was reported in a clinical study of the small molecule gamma-secretase inhibitor BMS-708163. Bryostatin has a different mechanism of action than antibodies directed at amyloid, but in the transgenic mouse model of AD treated with bryostatin a decrease of Aβ deposition was observed. Given the limited bryostatin experience in AD, the potential for ARIA and associated clinical events cannot be excluded. In NTRP101-202, however, there was no clinical evidence suggestive of vasogenic edema or microhemorrhage that required an MRI scan.

Subjects in this study, with moderately severe to severe dementia, are those who have had a progressive dementia to the degree that their activities of daily living and their ability to care for themselves may be compromised. Subjects with MMSE-2 scores of 15 or less display significant cognitive impairments that are disabling. Most if not all of these subjects will have progressed despite treatment and have no alternative treatments available. Based on the available nonclinical and clinical data, and the low risk of ARIA, the potential benefits of treatment with bryostatin at the proposed dose in this protocol outweigh the risks.

4.3 Study Endpoints

4.3.1 Safety Assessments

- Treatment emergent AEs and SAEs
- Vital signs, hematology, blood chemistry, and physical examination including body weight
- ECG parameters
- C-SSRS

4.3.2 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in the SIB total score assessment obtained after completion of the second course of treatment (Week 28).

4.3.3 Secondary Efficacy Endpoints

- SIB score at the end of the Week 42 follow-up visit, for subjects who completed week 42
- The change from baseline (screening) SIB total score at week 13
- The changes from baseline at Weeks 9, 20, 24 and 30 in the SIB total score
- The changes from baseline at Weeks 9, 13, 20, 24 and 30 in the SIB total score for subjects with baseline MMSE-2 scores of 10-14 and 15-18
- SIB trends over time; individual-specific slopes of total SIB scores will be obtained for all patients.

4.3.4 Exploratory Endpoints

- Change from baseline in ADCS-ADL-Sev total score at Weeks 13 and 42, for subjects who completed week 42

Change from baseline in MMSE-2 total score at Weeks 13 and 42, for subjects who completed week 42Change from baseline in NPI total score at Weeks 13 and 42, for subjects who completed week 42

4.4 Study Population

Subjects with moderately severe Alzheimer's disease defined as a MMSE-2 score of 10-18 inclusive are eligible to enroll. Subjects will be permitted to continue present FDA-approved treatments for Alzheimer's disease with the exception of memantine, but no new treatments can be initiated. OTC medications taken for cognitive improvement such as Ginkgo Biloba or other empiric medications are permitted while participating in the study but should not be initiated or dose modified after screening. Subjects who are no longer on medications for Alzheimer's disease can also be enrolled.

4.4.1 Inclusion Criteria

1. Written informed consent from caregiver and subject (if possible) or legally acceptable representative if different from caregiver
2. Male and female subjects 55-85 years of age inclusive
3. Cognitive deficit present for at least 2 years that meet the diagnostic criteria for probable Alzheimer's dementia.[16] The diagnosis must be confirmed at the time of the screening visit
4. MMSE-2 score of 10-18 inclusive (applies to Screening Visit only)
5. Patients must have a baseline SIB total score of at least 60 and may not have a SIB score >93 at screening
6. Neuroimaging computerized tomography (CT) or Magnetic Resonance Imaging (MRI) within the last 24 months consistent with a diagnosis of probable AD without any other clinically significant co-morbid pathologies. If there has been a significant change in the subject's clinical status since the last imaging study that is not consistent with progression of the subject's AD, an imaging study should be performed to confirm eligibility
7. Reliable caregiver(s) or informant(s) who attends the subject at least an average of 3 hours or more per day for 3 or more days per week and who will agree to accompany the subject to the clinic visits and reliably complete the caregiver questions
8. Adequate vision and motor function to comply with testing
9. If taking an approved cholinesterase inhibitor for treatment of Alzheimer's disease, must be on a stable dose for at least 3 months prior to entry into study and the dose must not change during the study unless a change is required due to an adverse effect of the prescribed medication or a clinically significant change in the patient's status

10. Subjects who are memantine naïve or have been off memantine for at least 90 days prior to initial treatment with study drug
11. Subjects on neuroleptic medications must be on a stable dose for ≥4 weeks (dose adjustments will be permitted)
12. Females participating in the study must meet one the following criteria:
    a. Surgically sterilized (e.g., hysterectomy, bilateral oophorectomy or tubal ligation) for at least 6 months or postmenopausal (postmenopausal females must have no menstrual bleeding for at least 1 year) or
    b. If not postmenopausal, agree to use a double method of contraception, one of which is a barrier method (e.g., intrauterine device plus condom, spermicidal gel plus condom) 30 days prior to dosing until 30 days after last dose and have negative human chorionic gonadotropin (β-hCG) test for pregnancy at screening
13. Males who have not had a vasectomy must use appropriate contraception methods (barrier or abstinence) from 30 days prior to dosing until 30 days after last dose
14. In the opinion of the PI subjects should be in reasonably good health over the last 6 months and any chronic disease should be stable

4.4.2 Exclusion Criteria

1. Dementia due to any condition other than AD, including vascular dementia (Rosen-Modified Hachinski Ischemic score ≥ 5)
2. Evidence of significant central nervous system (CNS) vascular disease on previous neuroimaging including but not limited to: cortical stroke, multiple infarcts, localized single infarcts in the thalamus, angular gyrus, multiple lacunar infarcts or extensive white matter injury
3. Clinically significant neurologic disease or condition other than AD, such as cerebral tumor, chronic subdural fluid collections, Huntington's Disease, Parkinson's Disease, normal pressure hydrocephalus, or any other diagnosis that could interfere with assessment of safety and efficacy
4. Evidence of clinically significant unstable cardiovascular, pulmonary, renal, hepatic, gastrointestinal, neurologic, or metabolic disease within the 6 months prior to enrollment If there is a history of cancer the subject should be clear of cancer for at least 2 years prior to screening. More recent history of basal cell or squamous cell carcinoma and melanoma in situ (Stage 0) may be acceptable after review by the Medical Monitor.
5. Creatinine clearance (CL) of <45ml/min
6. Poorly controlled diabetes, at the discretion of the Principal Investigator
7. Concomitant treatment with NMDA receptor antagonists such as but not limited to memantine or drug combinations containing memantine, dextromethorphan (a cough

suppressant), ketamine, phencyclidine (PCP), methoxetamine (MXE), nitrous oxide (N_2O) and the following synthetic opioids: penthidine, levorphanol, methadone, dextropropoxyphene, tramadol, and ketobemidone.

8. Use of vitamin E > 400 International Un its (IU) per day within 14 days prior to screening
9. Use of more than 2,600 mg/day of acetaminophen for more than 3 consecutive days within 14 days prior to screening
10. Use of gabapentin within 14 days prior to screening
11. Use of valproic acid within 14 days prior to screening
12. Use of an active Alzheimer's vaccine within 2 years prior to screening
13. Use of a monoclonal antibody for treatment of AD within 1 year prior to screening
14. Any medical or psychiatric condition that is likely to require initiation of additional medication or surgical intervention during the course of the study
15. Any screening laboratory values outside the reference ranges that are deemed clinically significant by the PI
16. Use of an investigational drug within 90 days prior to screening
17. Suicidality defined as active suicidal thoughts during the 6 months prior to screening or at Baseline [Type 4 or 5 on C-SSRS], or history of suicide attempt in previous 2 years, or at serious suicide risk in PI's judgment
18. Major psychiatric illness such as current major depression according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition[17], current or past diagnosis of bipolar disorder, schizophrenia, or any other psychiatric disorder that might interfere with the assessments of safety or efficacy at the discretion of the PI
19. Diagnosis of alcohol or drug abuse within the last 2 years
20. Abnormal laboratory tests that suggest an alternate etiology for dementia. If the patient has prior history of serum B12 abnormality, anemia with hemoglobin ≤10g /dl, thyroid function abnormality, electrolyte abnormality, or positive syphilis serology the patient should be revaluated to determine if these potential causes of dementia have been addressed. Only if these causes have been ruled out as the cause of the dementia can the patient be enrolled.
21. History of prolonged QT or prolonged QT on screening ECG (QTcB or QTcF >499 per central reader)
22. Acute or poorly controlled medical illness: blood pressure > 180 mmHg systolic or 100 mmHg diastolic; myocardial infarction within 6 months; uncompensated congestive heart failure [New York Heart Association (NYHA) Class III or IV][18]
23. Known to be seropositive for human immunodeficiency virus (HIV)
24. Known to be seropositive for Hepatitis B or C, unless successful curative treatment for Hepatitis C (e.g., Harvoni) has been received and there is documentation that there is no Hep B/C virus detected 3 months after completion of treatment

25. AST or ALT >3x upper limit of normal (ULN) and total bilirubin >2x ULN or International Normalized Ratio (INR) >1.5
26. Prior exposure to bryostatin, or known sensitivity to bryostatin or any ingredient in the study drug
27. Any other concurrent medical condition, which in the opinion of the PI makes the subject unsuitable for the clinical study.

5 PRODUCTS USED IN THIS STUDY

Active study drug, bryostatin, and a matching placebo will be provided as described below.

5.0 Bryostatin

The investigational drug product, bryostatin, is a sterile, pyrogen-free, lyophilized powder intended for IV infusion upon reconstitution and dilution. Bryostatin will be supplied in a 10 mL vial containing 0.025mg bryostatin, 2.5 mg povidone lyophilized from 40% t-butanol. Accompanying each vial of bryostatin will be a 10mL vial containing 2mL of sterile PET diluent [60% v/v polyethylene glycol 400, 30% v/v dehydrated ethyl alcohol, and 10% v/v Tween-80 (polysorbate 80)].

5.1 Placebo

The placebo is a sterile, pyrogen-free lyophilized powder intended for IV infusion upon reconstitution and dilution. It will be supplied in a 10 mL vial containing 0.0mg bryostatin, 2.5mg povidone lyophilized from 40% t-butanol. Accompanying each vial of placebo will be a 10 mL vial containing 2mL of the same sterile PET diluent as described above for bryostatin. The placebo is identical to bryostatin in appearance, including color, consistency, volume, and odor.

5.2 Packaging and Labeling of Study Drug Kits

Study drug kits will contain 7 vials of bryostatin for Infusion or 7 vials of placebo for Infusion and 7 vials of PET diluent. Each kit will be identified by kit number only and assigned to a subject via the Interactive Response Technology (IRT), according to the established randomization scheme.

Study drug kits will be labeled in English according to the US FDA's current Good Manufacturing Practice (GMP) and local regulations.

The kit label will contain the following information:

Bryostatin or Placebo for Infusion Kit

Kit # XXXXX

Store refrigerated at 2-8°C.

Caution New Drug - Limited by Federal Law (US) to Investigational use.

Each kit contains 7 vials Bryostatin for Infusion, 0.025 mg bryostatin/vial or 7 vials Placebo for Infusion, 0.0 mg bryostatin per vial and 7 vials PET Diluent

Manufactured for Neurotrope by Lyophilization Technology, Inc.

Study drug vials will be labeled in English according to US FDA's current Good Manufacturing Practice (GMP) and local regulations.

Bryostatin for Infusion or Placebo for Infusion vial label will contain the following information:

Bryostatin for Infusion, 0.025mg bryostatin or Placebo for Infusion 0.0mg bryostatin

Kit # XXXXX

Store refrigerated at 2-8°C

Caution New Drug - - Limited by Federal Law (US) to Investigational use.
Each vial contains 0.025mg bryostatin or 0.0 mg bryostatin and 2.5 mg povidone C-17. Contains no antibacterial preservatives

Reconstitute with 1 mL PET Diluent. Swirl to dissolve

Further dilute with 9 mL sodium chloride for injection

Manufactured for Neurotrope by Lyophilization Technology, Inc.

PET Diluent vial label will contain the following information:

PET Diluent for Reconstitution of Bryostatin for Infusion or Placebo for Infusion

Lot #: XXXX

Volume: 2 mL

Caution New Drug - - Limited by Federal Law (US) to Investigational use

Each mL contains Polyethylene Glycol 400 (60%), dehydrated Ethyl Alcohol (30%) and Polysorbate 80 (10%).

For Single Use Only

Manufactured for Neurotrope by Lyophilization Technology, Inc.

5.3 Storage and Preparation of Study Drug

The study drug kits will be stored under refrigeration conditions (2-8°C) in a refrigerator, refrigerated cabinet or other refrigerated enclosure, which is securely locked and temperature continuously monitored. Access to the stored study drug kits will be restricted to the investigational site pharmacy or designated staff member.

Study drug will be prepared and dispensed for administration by a qualified member of the study staff (e.g., pharmacist, pharmacist-designee, nurse or physician trained in aseptic handling techniques). This individual will be responsible for reconstitution, dilution and preparation of study drug (active and placebo) according to the randomization assignment for each subject. The investigational drug is to be administered only according to the conditions of this protocol.

Study drug will be administered by the study PI or his/her designees. Study drug should be allowed to come to room temperature prior to administration. The study drug contains no antibacterial preservatives and must be used within eight hours of reconstitution. Study drug should be reconstituted with 1mL of PET diluent. After swirling the 10 mL vial to completely dissolve the contents, the resulting solution must be diluted immediately with 9mL of 0.9% sodium chloride (NS) injection, USP. The necessary volume of this solution to achieve the assigned dose (a 9.6 mL loading dose for the first two doses and an 8.0mL maintenance dose for the remaining 5 doses) should then be added to an IV infusion bag containing 50 mL of normal saline. Once the infusion bag is filled with the assigned dose, the 45±5 minute continuous infusion must be completed within 3 hours of the IV infusion bag fill.

The infusion system (IV infusion bag and tubing) should be made of a polyolefin plastic, such as polypropylene or polyethylene, or a combination of both. The use of polyvinylchloride (PVC) plastic bags and tubing is NOT to be used as plasticizer from the PVC is leached and there is absorption of bryostatin to PVC plastics.

The prepared infusion bag containing study drug should be labeled with the following information:

Protocol number

Kit/Subject number

Date and time prepared

Instructions for dosing (*e.g.*, entire contents of IV infusion bag infused within 45 ±5 minutes

5.4 Study Drug Accountability and Disposal

Neither the Investigational Pharmacy, designated drug preparer, the PI nor any of his/her designees may provide drug to any person not enrolled in this study. Adequate records of study drug receipt and use must be maintained in order to comply with governmental regulations and with the protocol in addition to preventing unauthorized distribution.

Study drug orders, records of receipts, dispensing records, and inventory forms will be examined and reconciled throughout the study. All study drug that is used during the course of the study must be accounted for on a drug accountability form.

Unless otherwise directed, at the end of the study all unused study medication must be destroyed onsite following the site's specific SOPs after drug accountability has been verified by the monitor. If destruction on site is not possible, study medication should be retained and returned to Singota Solutions at the end of the study. A copy of all completed drug accountability forms will be collected by the monitor or appropriate designee upon completion of the study.

Note: The medications should not be disposed of prior to monitoring and approval.

5.5 Randomization

Once all eligibility criteria for the study have been met, and the site has received approval by the Medical Monitor (MM) and Clinical Assessment Technologies (CAT) group, via the EDC system, the subject can be randomized via Interactive Response Technology (IRT) system. Randomization will be stratified by SIB total score at baseline and baseline SIB scores will be balanced at baseline between the treatment groups. Mean values of baseline SIB total scores by group will be monitored in real time during the enrollment process. A randomization number will be assigned, and drug for that randomization number will be shipped to the site for twelve weeks of treatment. Randomization and scheduling of the first study drug infusion should be timed to allow for receipt of study drug prior to the scheduled study treatment. The drug kits will be shipped to the individual who will be responsible for kit storage and drug preparation and may not be handled by any other study staff member. The study drug kit will not identify the vial containing study drug as either placebo or bryostatin. After completion of Week 13, a second study drug kit will be provided for treatment period two. The IRT system will be used to register subjects for treatment and trigger study drug shipments.

5.6 Blinding

All subjects, PIs, and investigational clinical site personnel will be blinded to dose assignment. Since there is no known antidote to bryostatin, the blind should only be broken in exceptional circumstances and is at the discretion of the PI. The Medical Monitor should be contacted as soon as possible to discuss the situation, but this should not delay any treatment.

In a non-emergency situation, when unblinding is requested, the site should discuss the clinical circumstances with the Medical Monitor to determine if breaking the blind will alter the subject's treatment. The decision to break the blind is ultimately the decision of the PI. If the blind is broken for a subject, the PI will record the date and reason for breaking the blind in the electronic case report form (eCRF) and study drug treatment will be

discontinued. However, the subject will continue to be monitored per protocol for safety and efficacy.

5.7 Study Drug Administration

Study drug is scheduled to be administered by continuous intravenous infusion only, via a pump, at the same rate over 45 minutes (±5 min) once a week for 2 weeks and then every 14 days ±2 days thereafter. The same treatment schedule will be followed for treatment period two. The entire volume of study drug in the infusion bag is to be administered. Infusion times should not be extended or shortened. If a subject misses a dose, the dose should be administered as soon as possible. The subject should then continue on the original dosing schedule. Provided all efficacy assessments have been completed, if deemed necessary by the PI, a short acting sedative may be administered to reduce a subject's anxiety or agitation during the infusion. All medication is to be recorded on the Concomitant Medication eCRF.

6 STUDY PROCEDURES AND ASSESSMENTS

Subjects will be randomized to study drug, either bryostatin or placebo treatment. A follow-up visit will take place 30 days after the last dose of study drug for all subjects, including subjects that have discontinued treatment before completion of the study. Assessments will be performed according to the Schedule of Activities. (Table 1).

Table 1 - Schedule of Activities

NTRP101-204			Treatment Period 1									Treatment Period 2							1° End point	Follow-Up	
Week	**Screening**		**0**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30/FU**	**ET**
Day (±2 days)	**Days -28 to -2[d]**		**0**	**7**	**14**	**21**	**35**	**49**	**63**	**77**	**91**	**105**	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**210**	
Dose		**Rand**	**1**	**2**		**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**	**12**	**13**	**14**			
Informed Consent	X																				
Medical history[◊]	X																				
Demographics	X																				
Rosen-modified Hachinski Scale	X																				
SIB	X[Δ]						X*		X*		X	X*			X*		X*		X	X	X
MMSE-2	X						X*		X*		X				X*		X*		X		X
ADCS-ADL-Sev[b]	X						X		X		X				X		X		X		X
NPI[b]	X						X		X		X				X		X		X		X
CSSRS	X				X			X*			X			X*				X*			X
Labs^^	X				X			X*			X			X*				X*			X
ECG	X (x3)				X			X			X			X				X			
PE	X							X*[+]			X			X*				X*			X
Vitals	X		X[c]	X[c]	X	X[c]	X[c]	X[c]	X[c]	X[c]	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X
Randomization		X[a]																			
Confirm Eligibility	X[◊]	X										X									
Study Drug Dosing			X	X		X	X	X	X	X		X	X	X	X	X	X	X			
Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con meds	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Randomization after initial screening procedures indicate eligibility; [b] The ADCS-ADL-Sev and NPI may be administered via telephone at the discretion of the investigator, within the allowed time window for the scheduled visit; [c]Vital signs prior to infusion, then at 30, 60 and 90 minutes from start of the infusion (+/- 5min). [d]The visit window of ±2 Days does not apply to the Screening and Randomization period which is a maximum of 28 days. [◊] CT scan if necessary per inclusion criterion #6; [Δ]Baseline SIB administered during screening must be done within 3 weeks of the first dose of study drug. If the screening period exceeds 3 weeks, the SIB should be repeated on the day of first dose, prior to dosing;*before dose; ^^Labs: CBC including differential, coagulation, clinical chemistry, TSH at screening (T-3 and T-4 if TSH abnormal), CPK at screening and event of myalgia, βhCG if indicated, HbA1C if clinically indicated. [+] abbreviated physical examination.

6.0 Assessments

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the PI that may make it unfeasible to perform a test. In these cases, the PI must take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed, the PI will document the reason for the missed test and any corrective and preventative actions which were taken to ensure that the required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

6.0.1 Safety

Overall safety and tolerability will be assessed by the incidence of treatment emergent AEs and SAEs and by evaluations of change from baseline in physical examination, vital signs, 12-lead ECG, the C-SSRS, clinical chemistry, hematology, and coagulation lab tests.

6.0.1.1 Laboratory

Blood samples will be obtained for routine laboratory tests, including hematology, chemistry, coagulation and βhCG if indicated as outlined in the Schedule of Activities (Table 2).

Hematology tests will include CBC with differential, platelet count and coagulation (prothrombin time (PT) and partial prothrombin Time (PTT)) studies.

Clinical chemistry tests will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, estimated creatinine CL, glucose, calcium, CO2, total protein, albumin, ALP, ALT, AST, gamma glutamyl transferase (GGT) lactate dehydrogenase (LDH), uric acid and bilirubin. A serum creatine phosphokinase (CPK) will be done at screening and in the event of myalgia. A TSH will be done at screening, and T-3 and T-4 will be done if TSH result is abnormal.

Samples will be sent to a central lab for testing. Refer to the Laboratory Manual for detailed instructions.

6.0.1.2 Physical Examination

All physical examinations must be performed by the PI or qualified designee (physician, physician's assistant, or nurse practitioner). The complete physical examination conducted during the screening period and at designated subsequent time points should include, but is not limited to the following:

- General appearance
- Weight
- Height (screening only)

- Ears
- Eyes
- Nose
- Throat
- Neck
- Respiratory system
- Cardiovascular system
- Abdomen
- Musculoskeletal /Neurologic
- Extremities
- Skin
- Lymph nodes

An abbreviated PE will include but is not limited to the following:

- General appearance
- Weight
- Respiratory system
- Cardiovascular system
- Abdomen

Examination of other systems as needed to explore reports of AEs should be conducted as needed by the PI. Any clinically significant physical findings that were not present on the initial physical examination will be considered AEs and documented on the AE eCRF as well as in the subject's source documentation and on the physical examination eCRFs.

6.0.1.3 Vital Sign Measurements

Single supine blood pressure and pulse rate will be measured at Screening and at other visits as specified in the Schedule of Activities.

6.0.1.4 Electrocardiogram

An average of triplicate 12-lead ECGs will be collected at screening. The triplicate ECG measurements should be obtained approximately 2-4 minutes apart. Single 12-lead ECGs will be collected at time points specified in the Schedule of Activities.

6.0.1.5 Columbia Suicide Severity Rating Scale

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior. The scale should be administered by an individual with appropriate clinical training, who has also taken the specific rater training for the scale, which will be provided by an agent of the Sponsor prior to the study start. If at any visit from baseline on, there are "YES" answers on items 4, 5 or on any behavioral question of the C-SSRS, a risk assessment should be

done by a qualified clinician to determine whether it is safe for the subject to continue to participate in the study. A suicidality narrative should be constructed for subjects who have undergone any post-baseline risk assessment, using information from the C-SSRS, and available information from the NPI, prior screening and baseline information, the clinician assessment and the narrative guide. Subjects who answer "YES" on items 4, 5 or on any behavioral question of the C-SSRS on more than one occasion during a study should be discontinued from the study. Suicidality AEs or other clinical observations may, based on the judgment of the PI, also trigger a risk assessment and a narrative. When there is a positive response to any question on the C-SSRS, the PI should determine whether an AE has occurred.

6.0.2 Efficacy / Psychometric Assessments

All raters for the efficacy assessments need to be trained and qualified on the administration of the scales. A qualified rater is required for the administration of the SIB, NPI and MMSE-2.

The same qualified rater should perform a given Efficacy/Psychometric Assessment at approximately the same time of day for a given subject throughout the study. All changes in raters for a given assessments must be noted in the subject's source documents. The caregiver designated to provide assessments (ADCS-ADL-Sev and NPI) at the start of the study should be the same individual throughout the study. Should a change be necessary during the course of the study, the reason for the change and the first corresponding visit must be noted in the subject's source document.

All psychometric tests performed on study subjects on the same day should be administered in the following order: SIB followed by MMSE-2, except at the screening visit as described in Section 6.2.1. If the MMSE-2 score obtained at screening does not fall within the 10-18 range for inclusion, no further screening tests should be performed. Efficacy tests at subsequent visits should be administered prior to dosing.

6.0.2.1 Rosen-Modified Hachinski Scale

The Rosen-Modified Hachinski Scale will be evaluated at screening to differentiate Alzheimer's type dementia from multi-infarct dementia. The 8-item scale results in a score of 0-12; and a score of 5 or above is exclusionary for the study.

6.0.2.2 Severe Impairment Battery

The SIB is used to assess cognition in subjects with moderate and severe AD. It is divided into nine subscales that include attention, language, orientation, memory, praxis, visuospatial ability, construction, social skills, orienting head to name. Non-verbal responses are allowed, thus decreasing the need for language output. Forty questions are included with a point score range of 0-100. Lower scores indicate greater cognitive impairment.

6.0.2.3 Mini Mental State Examination, 2nd Edition

The Standard version of the MMSE-2, with two alternate forms, will be used. This version has the structure and scoring of the original 30-item MMSE-2 and scores are comparable. The MMSE-2 is a brief, widely used test for assessing overall cognitive state. The MMSE-2

measures selected aspects of cognition such as memory, orientation, attention, language, and praxis on a scale of 0-30. Lower scores indicate greater cognitive impairment.

6.0.2.4 Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory – Severe Impairment Version

The ADCS-ADL-Sev is a 19-item functional assessment of the performance of activities of daily living for subjects with moderate to severe Alzheimer's disease. Informants are queried via a structured interview format as to whether subjects attempted each item in the inventory during the previous 4 weeks, as well as their level of performance. Each item is rated from the highest level of independent performance to complete loss. Total score ranges from 0-54 with lower scores indicating greater functional impairment. The ADCS-ADL-Sev may be administered via telephone at the discretion of the PI, within the allowed time window for the scheduled visit.

6.0.2.5 Neuropsychiatric Inventory

The NPI is a caregiver interview-based rating scale assessing 10 behavioral disturbances occurring in dementia subjects. The NPI may be administered via telephone at the discretion of the investigator, within the allowed time window for the scheduled visit. Items are scored for both frequency and severity. Total scores range from 0-120 with higher scores indicating greater behavioral disturbances. For each item, the associated caregiver distress is also assessed.

6.1 Visit Procedures

6.1.1 Screening and Randomization (Days -28 to -2)

In order to avoid unnecessary screen failures, a prescreening telephone call to rule out clearly exclusionary conditions is advised prior to scheduling a screening visit. In addition, a Pre-Screening Consent form will be provided, allowing access to medical records prior to a subject's onsite screening visit. Use of this consent will reduce the occurrence of onsite screening visits by subjects ineligible for the study based on medical history. No study procedures will be performed under this preliminary consent. Informed Consent must be obtained before any study related procedures are performed. Screening procedures and randomization will take place within an approximate 4-week period prior to first dose administration (Days -28 to -2).
Subjects who are screen-failed (e.g. due to clinically significant laboratory abnormality or an active medical condition) may be re-screened if their medical condition stabilizes or improves as assessed by the PI. Subject who are screen-failed due to MMSE score may be rescreened in 3 months.
The Medical Monitor should be consulted prior to re-screening. Subjects who are Screen Failures may be rescreened only once.

The following procedures should be performed first at screening only to avoid unnecessary procedures for ineligible subjects:

- Collection of subject demographic data
- Review of concomitant medications
- Review of medical history

- Assessment of neuroimaging (CT or MRI performed within 2 years of screening)
- Evaluate Rosen-Modified Hachinski Scale
- Evaluate MMSE-2

After confirming that these parameters satisfy eligibility criteria, the remaining screening procedures should be performed;

- SIB. The SIB should be done within 3 weeks before the first study drug dose. If the screening period exceeds 3 weeks, the SIB should be repeated on the day of the first dose, prior to dosing. The repeat SIB score obtained closest to the day of dosing should be recorded in the eCRF as an unscheduled visit.
- NPI
- ADSC-ADL-SIV
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Blood samples for routine safety including hematology, PT, PTT, INR and serum-chemistry, CPK, TSH (T-3 and T-4 if indicated), and β-hCG, if indicated
- 12-lead ECG (x3)
- Complete physical examination
- Vital signs
- Adverse events and concomitant medications

If changes in the subject's health or mental status occur during the screening and randomization period, including changes in medication affecting the mental status, the Medical Monitor should be notified. The Medical Monitor will advise the PI regarding any assessments that should be repeated to ensure eligibility requirements are met.

Sites will not be able to randomize subjects before confirmation that eligibility criteria have been met per the review of the Rosen-Modified Hachinski Scale, MMSE-2, CSSRS, and other eligibility criteria by the Worldwide Clinical Trials' Clinical Assessment Technologies (CAT) group and Medical Monitor (MM).

6.1.2 Week 0 (Day 0 Dose 1)

If the subject has had no intervening medical issues or changes in medications between the date of randomization and Week 0, dosing may proceed as scheduled.

A final assessment of the inclusion/exclusion criteria, including any changes in medications or health status will be done before dosing to confirm the subject's eligibility.

The following procedures will be done on Day 0:

- *Dosing by IV infusion* will be done according to the procedures outlined in Section 5.7.
- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion

- Adverse events and concomitant medications

6.1.3 Week 1 (Day 7 ±2 days Dose 2)

One week after the first dose of study drug, subjects will return for a second infusion. The following procedures will be performed:

- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- AEs and concomitant medications

6.1.4 Week 2 (Day 14 ±2 days/ No dose)

- C-SSRS
- Blood samples for routine safety
- 12-lead ECG
- Vital signs
- Adverse events and concomitant medications

6.1.5 Week 3 (Day 21 ±2 days/ Dose 3)

- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.6 Week 5 (Day 35 ±2 days/ Dose 4)

- Prior to dosing:
    - SIB
    - MMSE-2
    - ADCS-ADL-Sev
    - NPI
- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.7 Week 7 (Day 49 ±2 days/ Dose 5)

- Prior to dosing:
    - C-SSRS
    - Blood samples for routine safety
    - 12-lead ECG
    - Abbreviated Physical exam
- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.8 Week 9 (Day 63 ±2 days/ Dose 6)

- Prior to dosing:
    - SIB
    - MMSE-2
    - ADCS-ADL-Sev
    - NPI
- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.9 Week 11 (Day 77±2 days/ Dose 7)

- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.10 Week 13 (Day 91 ±2 days)

At Week 13, subjects will undergo efficacy assessments as well as routine safety assessments. The following will be performed:

- SIB

- MMSE-2
- ADCS-ADL-Sev
- NPI
- CSSRS
- Blood samples for routine safety
- 12-lead ECG
- PE
- Vital signs
- Adverse events and concomitant medications

6.1.11 Week 15 (Day 105 ±2 days Dose 8)

The following will be performed:

- Prior to dosing:
  - SIB
- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.12 Week 16 (Day 112 ±2 days Dose 9)

- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.13 Week 18 (Day 126 ±2 days Dose 10)

- Prior to dosing:
  - C-SSRS

- Blood samples for routine safety
- 12-lead ECG
- Abbreviated Physical exam

- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.14 Week 20 (Day 140 ±2 days Dose 11)

- Prior to dosing:
  - SIB
  - MMSE-2
  - ADCS-ADL-Sev
  - NPI
- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.15 Week 22 (Day 154 ±2 days Dose 12)

- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.16 Week 24 (Day 168 ±2 days Dose 13)

- Prior to dosing:
  - SIB
  - MMSE-2

- ADCS-ADL-Sev
- NPI

- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.17 Week 26 (Day 182 ±2 days Dose 14)

- Prior to dosing:
  - C-SSRS
  - Blood samples for routine safety
  - 12-lead ECG
  - Abbreviated Physical exam
- Vital signs prior to infusion, then at 30(±5), 60(±5) and 90(±5) minutes from start of the infusion
- *Dosing by IV infusion*
- Adverse events and concomitant medications

6.1.18 Week 28 (Day 196 ±2 days)

- SIB
- MMSE-2
- ADCS-ADL-Sev
- NPI
- Vital signs
- Adverse events and concomitant medications

6.1.19 Week 30 (Day 210 ±2 days)

- SIB

- Vital signs
- Adverse events and concomitant medications

6.1.20 Early Termination

- SIB
- MMSE-2
- ADCS-ADL-Sev
- NPI
- CSSRS
- Blood samples for routine safety
- PE
- Vital signs
- Adverse events and concomitant medications

6.1.21 Follow-up Visits

- SIB
- Vital signs
- Adverse events and concomitant medications

6.1.22 Early Treatment Discontinuation and Follow-up

If for any reason, the investigator, subject or caregiver decide to discontinue the study drug or withdraw consent from the study, the subject and caregiver should be encouraged to complete an early termination (ET) visit and follow-up visit(s) as below:

- ET visit:
  - If the subject is withdrawn from the study at or before Week 13, subject will not enter Treatment Period 2.
  - If possible, schedule ET visits for 30 days (+/-2 days) after the last study drug dose administration
  - The ET reason must be documented with as much detail as possible in the EDC and in the source documents.

- Follow-up Visits: Despite discontinuation of the study drug dosing, subjects and caregivers should be encouraged to return for additional follow-up visits for the duration of the trial, in order to monitor for safety and any changes in cognition.
    - The follow-up visits should be scheduled to coincide with the cognitive assessment visits scheduled after the study drug discontinuation (i.e., weeks 5, 9, 13, 15, 20, 24, 28, 30).
    - The below assessments should be completed at all follow-up visits:
        - SIB
        - Vitals
        - Adverse Events
        - Concomitant medications
    - If the subject is willing to return for only one follow-up visit, please schedule this visit to occur approximately 30 days (+/-2 days) following the last study drug dosing.

6.2 Concomitant Medications

During the screening visit, the Caregiver will provide a history of prior medication use during the past 6 months and provide a list of currently used medications. All concomitant medications used should be recorded on the eCRF and in the source documents using the generic name for the drug. Assessment of concomitant medications will take place at each study visit. Any changes to chronic medications should be noted as well as new and discontinued medications.

Subjects taking allowed antidepressant medications may be enrolled in the study (see Appendix 1). The dose and dose regimen for these medications should be stabilized for at least 30 days prior to enrollment in the study. Every effort should be made to keep the dose and dose regimen of antidepressant medications stable throughout the study.

6.2.1 Medications for AD

Subjects taking FDA approved medications for the treatment of AD, **with the exception of memantine or any drug containing memantine**, may be enrolled in the study. The subject must be on a stable dose of permitted medications for at least 3 months prior to entry into the study and dose must not change during the study. Subjects may not initiate additional drugs for treatment of AD during the study other than the study drug.

6.2.2 Concomitant Medications for Management of Myalgia

Non-steroidal anti-inflammatory drugs such as ibuprofen and naproxen sodium are permitted. Use of acetaminophen as an analgesic is contraindicated as it has the ability to inhibit PKC activation.

6.2.3 Prohibited Medications

Memantine is prohibited. Subjects previously treated with memantine must stop treatment at least 90 days prior to initiation of study drug treatment. Treatment with other NMDA receptor antagonists such as but not limited to dextromethorphan (a cough suppressant), ketamine,

phencyclidine (PCP), methoxetamine (MXE), nitrous oxide (N_2O) and the following synthetic opioids: penthidine, levorphanol, methadone, dextropropoxyphene, tramadol, and ketobemidone is prohibited and a 30-day washout period is required prior to initiation of study drug treatment.

High dose Vitamin E (> 400 IU / day), Valproic Acid and divalproex sodium are prohibited.

Gabapentin is prohibited.

If the PI determines that initiation of any of the prohibited medications is required to ensure the subject's safety, the medication may be initiated with the notification of the Medical Monitor and proper documentation of a protocol deviation. Other restricted concomitant medications are listed in Appendix 1.

7 ADVERSE EVENTS AND OTHER SAFETY EVALUATIONS

7.0 Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

The PI is responsible for obtaining information about all medical emergencies during the clinical study. The PI's contact information will be located in the body of the informed consent form (ICF) and subjects/caregivers will be encouraged to contact the PI or clinical site personnel during any clinical study-related emergency.

All adverse events spontaneously reported by the subject and/or caregiver in response to an open question or revealed by observation will be recorded during the study regardless of relationship to the study drug. All AEs will be monitored and recorded for the progress of the event until it resolves or reaches a clinically stable outcome. Adverse events that are not resolved at the time of database lock will be recorded as ongoing.

The AE and SAE reporting period starts from the time of consent to the last study visit.

7.1 Adverse Event of Special Interest - Myalgia

Myalgia has been reported as the dose limiting toxicity across the oncology studies. The incidence of myalgia appears to be dose dependent and cumulative. However, it has been reported in subjects receiving doses as low as 5µg/m^2. The myalgia has been investigated in some studies but not all. No increase in muscle enzymes were found in the cases investigated. EMG was abnormal in one subject who received 65µg/m^2 and suggested a patchy myositis. An MRI done in another subject was normal.

For all cases of myalgia despite the severity, a narrative will be created documenting onset, severity, treatment and outcome. Muscle enzymes, CPK, will be collected for all cases and compared to baseline values. Additional investigations are at the discretion of the investigator.

7.2 Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that fulfills any of the following criteria:

- Results in death (fatal)
- Is life threatening (an event is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence placed the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

or

- Is an important medical event (events that may not result in death, be immediately life threatening or require hospitalization; may be considered serious when based upon appropriate medical judgment, they jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples include; allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

The following situations may not, by themselves, constitute sufficient grounds to be considered as an SAE:

- Hospitalization solely for a diagnostic purpose, even if related to an AE,
- Elective hospitalization for an intervention planned before the subject enrollment in the study
- Admission to a day care facility or sleeping laboratory

7.3 Assessment of Intensity

Severity is a clinical determination of the intensity of an AE and will be determined by the PI based on the following classification criteria for all AEs occurring during the clinical study:

Mild - Awareness of signs or symptom, but easily tolerated, may require additional therapy

Moderate - Discomfort, enough to cause interference with usual activity and to require intervention or additional therapies

Severe - Incapacitating with inability to work or perform usual activity

Note: It should be noted that a severe AE need not be serious in nature and that an SAE is not, by definition, severe. Regardless of intensity, all SAEs and significant events must be reported.

7.4 Relationship to Study Drug

The causal relationship between the investigational drug and each AE will be determined by the PI based on his/her medical judgment in consideration of all relevant factors, including pattern of reaction, temporal relationship, positive, concomitant medication, co-existing diseases, and relevant medical history. The PI will classify every AE according to its relationship to study drug or trial-related procedures. The categories according to World Health Organization guidelines are listed in the following Table

7.5 Table 2 Relationship of AE to Study Drug or Trial-Related Procedures

Rating	Classification	Definition
1	Probable	An AE that: • Occurs at a reasonable time interval after administration of the study drug; • Follows a known response pattern to the study drug and; • Cannot be reasonably explained by the known characteristics of the subject's clinical state or by other therapies.
2	Possible	An AE that: • Occurs at a reasonable time interval after administration of the study drug; • Follows a known response pattern to the study drug, but; • Could have been produced by the subject's clinical state or by other therapies.
3	Unlikely*	• An AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug; • Another etiology is specified.

*If the AE is classified as unlikely, the PI should provide a likely cause, other illness, concomitant medication, or other.

7.5.1 Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed. Unexpected refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug

under investigation. However, an event that is more specific or more severe than described in the IB will be considered unexpected.

7.6 Reporting Adverse Events

The PI should instruct all subjects/caregivers on the procedure for reporting AEs/SAEs to the appropriate clinical site personnel. For each AE reported by parents/guardians, clinical site personnel should obtain all required information to complete the eCRF.

The PI or designee should document all AEs/SAEs in subjects' source documentation and on the AE eCRF.

In addition to standardized reporting procedures, worsening or exacerbation of concurrent conditions in subjects will also be reported as AEs, and will follow the designated reporting format.

The following should be recorded with each SAE/AE:

- The nature of the AE, with a diagnosis wherever possible
- Date of event
- Assessment of intensity
- Is this an SAE?
- Relationship to study drug or trial-related procedures
- Action taken regarding study drug treatment
- Outcome

If the intensity of an already reported AE increases, then a new AE eCRF must be completed for that AE. The date of change would be included as the end date for the originally reported AE, and the start date for the new AE of greater intensity.

The clinical research associate is responsible for source document verification of all safety events.

If the clinical site becomes aware of an SAE, regardless of causality, within 30 days following the last administration of investigational product, the SAE should be recorded and reported immediately to the Sponsor. An SAE that occurs more than 30 days after the last dose will NOT be collected unless the PI considers that the event is related to the investigational product.

The sponsor should be informed if the PI becomes aware of any unusual safety information or any potential drug-related safety information, even after a subject completes the study

7.6.1 SAE reports

All SAEs, whether or not considered associated with study treatment or study-related procedures, must be reported on the eCRF immediately and no later than 24 hours after the site becomes aware of the event. Follow-up information must be provided promptly as requested.

The PI is obligated to provide as much information about the event as possible on the eCRF provided and as requested by the Sponsor or Medical Monitor.

In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case. The pharmacovigilance physician or designee will review the SAE including the SAE criteria, the relationship to study medication, the expected or unexpected assessment, and inform the Sponsor by phone and e-mail immediately.

The following AEs should also be reported to the Sponsor's designated Medical Monitor immediately:

- severe injection/infusion site reactions (ulceration or necrosis that is severe; operative intervention indicated)
- systemic hypersensitivity reactions
- myalgia

All additional follow-up evaluations must be reported by the site to the medical monitor, or designee, immediately after notification of the additional information.

An SAE will be followed until it resolves or reaches a clinically stable outcome. AEs/SAEs that have not resolved by study closure will be considered ongoing.

An SAE that occurs after the 30-day safety visit will NOT be collected unless the PI determines that the event is related to the investigational drug product.

7.6.2 Reporting to Regulatory Authorities

The PI, or designee, is responsible for informing the Institutional Review Board (IRB) of any unexpected SAEs, as well as any additional SAEs according to the IRB's policy.

Any SAE that is serious, suspected to be related to investigational study drug and unexpected (SUSAR), will be promptly reported to regulatory authorities by the Sponsor according to expedited reporting requirements. Subsequent relevant information after the initial submission of the (IND) Safety Report to the regulatory authorities will be submitted in a follow-up IND Safety Report to the regulatory authorities in the expedited period by the Sponsor.

7.7 Criteria for Withdrawal of Subjects

Subjects may be withdrawn from the clinical study for the following reasons:

- The PI believes withdrawal to be medically necessary or in the best interest of the subject
- Noncompliance with the protocol as judged by the PI (requires discussion with the Sponsor)
- Subjects who are enrolled in violation of inclusion and/or exclusion criteria
- An AE that presents an unacceptable consequence or risk to the subject as judged by the PI, Sponsor or the Medical Monitor
- Lost to follow up
- Withdrawal of consent

- Subject is unblinded

Subjects may voluntarily discontinue their participation in the study at any time without prejudice to further treatment.

7.8 Criteria for Permanent Discontinuation of Study Drug

Study drug treatment may be discontinued for the following reasons:

- if sponsor or regulatory authorities discontinue study
- if the PI believes that discontinuing treatment is in the best interest of the subject

7.9 Study Discontinuation

Synaptogenix has the right to discontinue this clinical study at any time. The PI has the right to discontinue participation in this clinical study at any time for any reason. Clinical study site discontinuation should only occur after mutual consultation between the PI and Synaptogenix.

Should the clinical study be discontinued prematurely, all subjects should be brought in for early termination procedures as outlined for the 30-day Follow-up visit. All clinical study materials should be returned to Synaptogenix or designee.

8 SAFETY MONITORING

A Data Safety Monitoring Board (DSMB) will provide consultation to Synaptogenix to assess the implementation and progress of study NTRP101-204 and will review accumulating trial data to monitor the safety of bryostatin administered to patients with AD. Safety data will be reviewed when 30 subjects have received four doses of study drug, followed by additional safety analyses when 60 subjects have received a similar number of doses. Medical decisions relevant to this study will be made by the Sponsor in consultation with the Primary Investigator, Medical Monitor and Statistician.

Prior to each safety review, a cut-off date for the data to be provided will be established by the Sponsor in consultation with the WCT Supporting Biostatistician. The format and content of data listings will be approved by the Supporting Biostatistician. Data reports will be provided as partially blinded displays (e.g., data is grouped by unblinded treatment using "Group A, B" to indicate treatment). The identity of each group will be available to the safety reviewer via the Supporting Statistician.

Data review documents, safety data tables and listings, will be provided to the DSMB at least 7 business days prior to scheduled reviews. Serious Adverse Events (SAEs) reported during the 7 days before the scheduled review and therefore not included in the provided documentation will be provided by the WCT Drug Safety Manager as soon as possible before the review date. The reviews of the safety data will be summarized for the overall subject group only and will not be separated by treatment groups.

9 DATA ANALYSIS / STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). This separate document will be finalized prior to study unblinding and conduct of any statistical analyses. The SAP may modify and will take precedence over the plans outlined in the protocol; however, any major modifications or modification of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

The primary efficacy outcome will be the difference in SIB total score from baseline at Week 28 between treatment arms, after two12-week courses of the study drug have been given.

9.0 Sample Size Determination

The power analysis for the current study is based on a minimum clinically significant difference in mean total SIB scores from baseline of 4 points between the placebo and bryostatin arms at Week 28. Since the analysis of this primary outcome is based on a linear regression model that utilizes the total SIB scores at Weeks 0, 5, 9, 13, 15, 20, 24, and 28, a difference of approximately 1.5 points per week in the slope of total SIB scores between the placebo and bryostatin arms yields the clinically meaningful difference of 4 points at Week 28. As these measures of total SIB scores are correlated within individual, methods of GEE will be used to estimate the regression parameters of the linear regression model of total SIB score regressed on time. GEE power analysis is based on the following equation:

$$m = \frac{2\left(z_{a/2}+z_b\right)^2\sigma^2(1-\rho)}{ns_x^2d^2} \qquad \text{Eq 1}$$

In equation 1, m is the number of patients per group, $z_{a/2}$is the type I error rate, $z_b$is the type II error rate, σ is the standard deviations of the error (residual) terms, ρ is the within person correlation of total SIB scores over time within a person, n is the time points where the total SIB score is obtained, $s_x^2$is the variance of the X predictor variable (i.e. time in the current scenario), and d is the difference in slopes over time in total SIB measures from baseline between the placebo and bryostatin arms.[17]

Based on the data from the NTRP101-202 study among patients without memantine, we obtained an estimate for σ = 5.3. In addition, the NTRP101-204 study will have SIB total scores measured at n = 8 timepoints, giving a value of s_x^2 = 127. Assuming a total of 100 patients (50 patients per arm), a two-sided type I error rate of 0.05 (i.e. $z_{a/2}$ = 1.96), and moderate within person correlation of outcome measures (i.e. ρ = 0.5), we will have > 99% power to see a difference in slopes over time of d = 0.15 points per week. In addition, we will have > 99% power to see this difference if we experience a 20% drop out.

9.1 Statistical Methods

The Safety Analysis Set (SAS) is defined as all randomized subjects who received any study medication (either partial or completed infusions of bryostatin or placebo).

The Full Analysis Set (FAS), consistent with the modified intention-to-treat (mITT) principles, is defined as all randomized subjects who received at least one dose of study medication and who have at least one post-baseline efficacy assessment.

The Per Protocol Analysis Set (PP) is defined as all patients completing the study without major protocol deviations. To be included, subjects must have received at least 11 of the14 doses (80%).

The Completer Analysis Set (CAS) is defined as all randomized subjects who completed two courses of treatment, and who have a week 28 SIB assessment.

Demographics data collected will include age, sex, race, ethnicity, height, and body weight and will be summarized by treatment group using descriptive statistics for both the SAS and FAS populations.

Medical history, neuroimaging, prior and concomitant medications, existing disease, years since AD onset and diagnosis, baseline medical conditions, and baseline safety and neuropsychological assessments will be summarized descriptively by treatment group for both the SAS and FAS populations.

Subject disposition will be summarized by treatment group and will include numbers screened, randomized, dosed and withdrawn with reason for withdrawal.

9.2 Exploratory Analysis

Descriptive statistics by visit and randomized treatment group will be provided for all efficacy data. These descriptive statistics will include the mean, median, SD, maximum and minimum for continuous variables, and frequencies, percentage, and tabulations for categorical variables. Summary statistics will also be performed on both the patient demographics and patient clinical characteristics. Exploratory plots of the data will also be created, including box plots and histograms, in order to determine the distribution of these data as well as to identify any unusual or outlying observations.

9.3 Safety Analysis

The SAS population will be used for all safety analyses with treatment group determined by the treatment actually received. AEs, safety laboratory, ECGs, physical exam and vital signs data will be presented in tabular format and summarized descriptively by treatment group. No formal hypothesis testing will be carried out on these safety assessments. Incidence and severity of AEs will be summarized by treatment dose using System Organ Class (SOC). AEs will be coded according to standard MedDRA terms.

C-SSRS responses will be mapped onto the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) scale, and the frequency distribution of the C-CASA scores will be tabulated by treatment group and study visit. No hypotheses associated with the C-SSRS or C-CASA scales will be tested.

9.4 Analysis of Primary Efficacy Endpoint

The treatment difference in the primary efficacy endpoint of total SIB scores from baseline at Week 28 will be determined from a regression model that utilize SIB values taken at Weeks 0, 5, 9, 13, 15, 20, 24, 28 and 30. As SIB is a continuous outcome measure, a regression model will be used to estimate the treatment difference in mean SIB from baseline at Week 28. Both linear and non-linear terms will be considered in these regression models. Since correlation of SIB measures over time within a patient will be present, regression coefficients will be estimated using the generalized estimating equations (GEE) methodology.[18] GEE regression models are used to appropriately estimate the population average effects from a sample of individuals when the correlations of SIB measures within individuals are unknown. The GEE method accounts for the correlation structure in the model. However, the estimates of model coefficients and their standard errors models are unbiased even if the working correlation model is incorrectly specified. The primary analysis will be conducted on FAS population. The PP and CAS populations will be used as supportive analyses. All statistical tests for efficacy will be two-sided tests, with α=0.05.

Based on the review of patients not treated with memantine in the NTRP 101-203 clinical trial, the expected number of patients who will drop out of the study prematurely will not be significant. However, missingness will be accounted for using weighted GEE methods.[19] The GEE regression models will be carried out in SAS/STAT PROC GEE version 13.2. This SAS procedure will allow for implementation of weighted GEE methodology that can account for data missing a random. One additional patient may be randomized for each patient who discontinues the study prior to the primary endpoint (Week 28, Day 196).

9.5 Secondary Efficacy Endpoints

Multiple comparisons arising from the listed secondary outcomes will be controlled by using the false discovery rate. This procedure will allow control of the type I error rate over the set of secondary outcomes that is less stringent then controlling for multiple comparisons using a familywise error rate (e.g. Bonferroni correction).

9.5.1 SIB total score from baseline at the Week 42 follow-up visit

Treatment differences in SIB total score from baseline at Week 42, for subjects who completed that visit, will be estimated using an ANCOVA model that will adjust for baseline SIB total scores, baseline MMSE-2 scores, age, and gender.

9.5.2 SIB total score from baseline at Week 13

An ANCOVA model as described in Section 9.5.1 will be created to estimate the difference in SIB total scores at Week 13. Again, as with the SIB difference at Week 42. The ANCOVA model will adjust for baseline SIB, baseline MMSE-2 scores, age, and gender.

9.5.3 SIB total scores from baseline at Weeks 9, 20, 24 and 30

The linear regression models using the method of GEE as described in Sections 9.4 and 9.5.2 will be used to estimate the treatment difference in mean SIB total scores from the original baseline (i.e. at screening) at Weeks 9, 20, 24 and 30. As described in Section 9.4, weighted GEE will be used to account for data that are missing at random.

9.5.4 SIB total scores from baseline at Weeks 5, 9, 15, 20, and 24 for subjects with baseline MMSE-2 scores of 10-14 and 15-18

The estimation of the treatment differences at Weeks 9, 20, 24 and 30 for patients within each MMSE-2 group will be based on GEE linear regression model utilizing SIB total scores from baseline at these five time point**s.** As described in Section 9.4, weighted GEE will be used to account for data that are missing at random.

9.5.5 Individual patient's SIB trends over time

For the secondary endpoint of SIB trends over time, individual-specific slopes of total SIB scores will be obtained for all patients. These slopes will be estimated by using SIB data at Week 0, 5, 9, 13, 15, 20, 24, and 28. An overall population averaged slope will then be estimated for each treatment arm, and standard inference methods will be used to test if the mean treatment-specific slopes are 1) statistically different from 0, and 2) statistically different from each other. Both slopes will be considered using absolute SIB total scores as well as SIB total scores from baseline over Weeks 0 to 28.

9.6 Analysis of Exploratory Endpoints

The following exploratory endpoints will be analyzed:

- Change from baseline in ADCS-ADL-Sev total score at Week 13 and Week 42, for subjects who completed week 42
- Change from baseline in MMSE-2 total score at Week 13 and Week 42, for subjects who completed week 42
  Change from baseline in NPI total score at Week 13 and Week 42, for subjects who completed week 42

Similar analysis methods that incorporate the method of GEE as described under the analyses for the primary and secondary endpoints will be used for analysis of the exploratory endpoints.

9.7 Safety Assessments

Unblinded summaries and listings of safety data will be provided to the Data Safety Monitoring Board, as described in Section 8. Analyses will be performed by an independent unblinded statistician so that study investigators and other sponsor personnel (and contractors) involved in study monitoring, data processing and other aspects of the study remain blinded.

9.8 Analysis of Safety Data

For continuous variables, data will be summarized by treatment using n, mean, SD, minimum and maximum values. For categorical variables, data will be summarized by treatment using frequency and percentage.

9.8.1 Adverse Events

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall (*i.e.,* regardless of severity or relationship to treatment)
- By severity grade (mild, moderate, severe, life threatening or death for SAEs)
- By relationship to clinical trial treatment (definitely related, probably related, possibly related, unlikely related, unrelated)

Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

AEs leading to premature discontinuation of clinical trial treatment, AEs that lead to study discontinuation, AEs that lead to death and Serious Adverse Events (SAEs) will also be summarized by treatment group and relationship.

9.8.2 Clinical Laboratory Evaluations

All available results of the clinical laboratory evaluations will be listed and summarized as follows:

9.8.2.1 *Laboratory Values over Time*

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented by treatment group and time point. Data will be summarized as appropriate for the variable type.

- For continuous data, summaries will include the number of observations, mean, SD, median, minimum, and maximum values.
- For categorical data, frequency counts and percentages will be used.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

9.8.2.2 *Individual Subject Changes (Shift Tables)*

Individual subject changes will be identified through shift tables. Shift tables will be presented for each laboratory parameter with counts and percentages of subjects, by treatment group and time point, for shift (change) from baseline, using the normal ranges from the laboratory.

9.8.2.3 *Individual Clinically Significant Abnormalities*

Clinically significant laboratory abnormalities (i.e., those laboratory abnormalities recorded as AEs) will be listed.

All results of laboratory evaluations will be presented as by-subject listings.

9.8.3 Physical Examination

All physical examination findings will be listed and/or summarized by treatment group. Shift tables will also be presented to show any abnormality shifts from baseline to post baseline visits.

9.8.4 Vital Signs

Tabulations of raw data and change from baseline values will be presented by time point for each vital sign parameter.

Tabulations will include the number of observations, mean, standard deviation, median, and minimum and maximum values. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

9.8.5 ECG

All ECG findings will be listed and/or summarized. Shift tables will also be presented to show any abnormality shifts from baseline to post baseline visits.

9.8.6 Columbia Suicide Severity Rating Scale (C-SSRS)

All data from C-SSRS will be listed. Descriptive summaries will be presented for each of the subscales (i.e. Suicidal Ideation and Suicidal Behavior).

10 DATA MONITORING

10.0 Source Documentation

In accordance with ICH-GCP guidelines, source documents may include, but are not limited to the following:

- Clinic, office, hospital charts
- Copies of transcribed health care provider notes, which have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays and other imaging reports, sonograms, computed axial tomography scans, magnetic resonance images, radioactive images, electrocardiograms, electroencephalograms
- Records of telephone contacts
- Diaries, evaluation checklists, or questionnaires that are completed directly by subjects or caregivers and serve as their own source
- Laboratory results and other laboratory test results
- Correspondence regarding a subject's treatment between physicians or memoranda sent to the IRB.

10.1 Study Documentation and Record Retention

The PI, or designees, must enter all results collected during the clinical study into eCRFs. eCRF completion guidelines will be reviewed with clinical site personnel at the PI's Meeting and site initiation visits. PIs are responsible for approval of all entered or corrected data. The PI, or designees, must review and approve the data before database lock, or before any scheduled interim analyses, as required by the sponsor.

The medical records (source documents) upon which the eCRFs are based must be kept at the clinical site for at least a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified. Synaptogenix must be informed if the records are passed on to any other person or institution during this period. Records related to the study will be maintained by Synaptogenix or its designee for a minimum of 5 years per 21 Code of Federal Regulations (CFR) 58.195 (b) 2.

10.2 Site Monitoring

The Sponsor or its designee will be allowed to conduct site visits at the investigation facilities to monitor any aspect of the study. The PI will provide Synaptogenix, or its designee, with documentation of IRB approval of the Study Protocol and the Informed Consent prior to study initiation and IRB approval of any subsequent amendments to the protocol or revision to the Informed Consent. Before a study site can enter a subject into the study, the Sponsor or a designee will:

- Determine the adequacy of the facilities
- Discuss with the PI(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Synaptogenix or its representatives. This will be documented in a clinical study agreement between Synaptogenix and the PI.

During the study, a monitor from Synaptogenix or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the PI(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Synaptogenix
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been reported and those SAEs that met criteria for reporting have been forwarded to the EC/IRB/ Independent Ethics Committee (IEC).
- The monitor will be responsible for immediately reporting any site not adhering to the study protocol to the project manager and Sponsor. Noncompliance may result in site suspension or closure.

The monitor will be available between visits if the PI(s) or other staff needs information or advice.

10.3 Quality Assurance and Quality Control

To ensure compliance with GCP and all applicable regulatory requirements, Synaptogenix, Inc. or its representative may conduct a quality assurance audit.

10.4 Audits and Inspections

Authorized representatives of Synaptogenix, a regulatory authority or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The PI should contact Synaptogenix immediately if contacted by a regulatory agency about an inspection.

11 ETHICS

11.0 Institutional Review Board

The PI must obtain IRB approval before initiating any study activities.

The final study protocol, including the final version of the Informed Consent Forms, must be approved in writing by an IRB. The PI must submit written approval to Synaptogenix or its representative, before he or she can enroll any participant into the study.

The PI is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from this or any other study conducted with the investigational product. Synaptogenix, will provide this information to the PI.

In addition to SAEs that are suspected unexpected serious adverse reactions (SUSARs), the PI or designee will report any additional SAEs that may be required according to the IRB policy.

Progress reports will be provided to the IRB according to local regulations and guidelines.

11.1 Ethical Conduct of the Study

The conduct of this study will be consistent with ICH Guidance E6, GCP, and U.S. federal regulatory requirements, as applicable. This study will be conducted in accordance with applicable local law(s) and regulation(s) and the principles of protection of healthy human subjects participating in clinical medical research that have their origin in the Declaration of Helsinki. The PI must agree to the direct access to source documents and inspection of clinical study-related records by the regulatory authority/Synaptogenix representatives.

11.2 Written Informed Consent

Written informed consent must be obtained from caregiver and subject (if possible) or legally acceptable representative if different from caregiver. A pre-screening consent, allowing access to medical records in advance of the on-site screening visit, will be provided for this study. The purpose of this consent, which must be IRB-approved before use, is to avoid unnecessary site visits by subjects whose medical history excludes them from eligibility. The pre-screening consent and medical record review is not required but strongly recommended.

The PI should confirm to the extent possible that the subject has the necessary caregiver support and will be able to attend scheduled study visits for the duration of the study.

Before starting the clinical study, the PI must have the IRB's written approval or favorable opinion of the written ICF and any other written information to be provided to parents or guardians of subjects. The written approval of the IRB together with the approved subject's

information/ICF must be in the clinical study files. The process of obtaining informed consent must be in accordance with applicable regulatory requirements and must adhere to ICH E6(R1) guidelines and the ethical principles in the Declaration of Helsinki. Written informed consent must be obtained and documented before any clinical study-specific procedure takes place. Participation in the clinical study and dates of informed consent given by subjects should be documented in the subjects' files.

12 STUDY MANAGEMENT

12.0 Data Collection and Management

For all written documentation such as source documents, the data collected during the study must be legibly printed using a permanent ink pen. A single line should be drawn through any incorrect information. Opaque correction fluids or tapes are not permitted. All corrections or deletions to any of the source documents must be dated and initialed. All corrections or deletions to the eCRF will be documented via an electronic audit trail. The PI or designee will electronically sign each subject's final eCRF to signify that all of the information is correct and complete.

12.1 Data Quality Control

Periodic on-site review of communications between the PI and investigational site study monitors, and review of eCRF data and source documents are the responsibility of the Sponsor, or designee. The eCRF data for each subject will be reviewed against source documents at the study sites by the investigational site study monitor.

The PI and investigational site will allow study related quality control monitoring and audits, EC/IRB/IEC review, and/or regulatory inspection and will cooperate in providing direct access to source data and documentation.

12.2 Data Management and Data Storage

Study procedures will be documented on source documents that will be retained at the site(s). An Electronic Data Capture (EDC) system will produce eCRFs that will be used to collect assessment data for this study. All study data entered into the eCRF will be compliant with regulatory requirements and 21CFR part 11. The system will allow differing levels of access and will accommodate roles for the PI, Medical Monitor, CRO, and Sponsor. All data changes made within the system will be subjected to an audit trail. In compliance with GCP, source documentation supporting the eCRF data should indicate the subject's participation in the study and should clearly document the dates and details of study procedures, AEs, and subject status. The eCRFs will identify study subjects with unique identifiers. Data are recorded from the source documents, directly onto the eCRF at the site.

Electronic CRF data items will undergo quality control standards of operation. Unresolved errors, omissions, or requests for clarification will trigger a query to the Investigational Site for resolution via electronic queries. The database will be corrected for completeness and accuracy.

Prior and concomitant medications will be entered into the eCRF and coded using the World Health Organization Drug Reference List (WHO-DRL). Medical history, concurrent medical conditions, and AEs will be coded using MedDRA.

A quality assurance audit will be conducted to verify the accuracy and completeness of the database and will be done prior to declaring database lock. The database will not be altered after lock, unless joint written agreement is obtained between the CRO and the Sponsor.

12.3 Inspection of Records

Synaptogenix, Inc., will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The PI agrees to allow the monitor to inspect the drug storage area, study drug stock, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

12.4 Retention of Records

A searchable offline version of the eCRF will be forwarded to the Sponsor for storage. A copy of each completed eCRF will remain in the PI's study file on a compact disk. All source documentation, eCRFs and administrative records will be retained by the PI for a minimum of 2 years following agency approval of the medication for the indication under study or following notification that the investigational application is closed for this indication. However, this may be adjusted based on the applicable local requirements. After this time, the documentation will either be destroyed or transferred to Synaptogenix or designee. No study documentation should be destroyed or moved to a new location without prior written approval by Synaptogenix.

12.5 Confidentiality

All study findings and documents will be regarded as confidential. The PIs and members of their research teams must not disclose such information without prior written approval from Synaptogenix or its representatives.

The anonymity of participating subjects must be maintained. A Protected Health Information statement will be provided to each subject either as a part of the Informed Consent document or as a separate form. Subjects will be identified on eCRFs and other documents by their initials, birth date, and subject number. Documents that identify the subject by name (e.g., the signed Informed Consent Form) must be maintained in strict confidence by the PIs.

12.6 Protocol Amendments

Minimally, any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study will be effected by means of a protocol amendment approved by the Sponsor. Any changes that affect subject safety or welfare must be submitted to the relevant IRB and approved before implementation.

The PI will provide written agreement of the protocol amendment via the approval signature page. The PI will notify the IRB of the amendment and obtain approval prior to implementation.

If the change is intended to eliminate an immediate hazard, the amendment will be implemented immediately, prior to IRB notification.

12.7 Protocol Deviations

Should a deviation from the protocol be deemed crucial for the safety and well-being of a particular subject, such a deviation will be instituted for that subject only. The PI or other attending physician should contact the Medical Monitor as soon as possible. In addition, the PI or designee should document in the source document the reasons for the protocol deviation and the ensuing events. No protocol deviations for any Inclusion or Exclusion criterion will be permitted in this study.

12.8 Data Corrections

For all written documentation such as source documents, the data collected during the study must be legibly printed using a permanent ink pen. A single line should be drawn through any incorrect information. Opaque correction fluids or tapes are not permitted. All corrections or deletions to any of the source documents must be dated and initialed. All corrections or deletions to the eCRF will be documented via an electronic audit trail. The PI will electronically sign each subject's final eCRF to signify that all of the information is correct and complete.

12.9 Insurance

The Sponsor has taken out a liability insurance policy, which covers the liability of PIs. This policy is in accordance with local laws and requirements.

The Sponsor's insurance does not relieve the PI or the collaborators of any obligation to maintain their own liability insurance policy as required by the applicable law.

13 PUBLICATION AND DISCLOSURE POLICY

Study findings are an integral part of the overall commercialization plan for this investigational compound. To this end, the contents of this protocol and any amendments and results obtained during the study shall be kept confidential by the investigator, the investigator's staff, and the IRB/IEC, and shall not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the review and prior written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the Sponsor/CRO. Additionally, the publication plan of the Sponsor, considering, among other items, proprietary patent issues and competitive strategic goals, must be complied with prior to the public disclosure of any aspect of this study by abstract, verbal presentation, invited lecture, journal article, or journal letter.-Matters regarding authorship and the order of authorship on publications reporting the results of single study findings are covered in a separate agreement.

14 APPENDIX 1 - RESTRICTED CONCOMITANT MEDICATIONS

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Chronic Use	Restrictions
Analgesics	(Y)	(Y)	Only non-opioid containing analgesics can be administered chronically. Use of acetaminophen as an analgesic is contraindicated as it has the ability to inhibit PKC activation. However, prn administration for pain may be used with a maximum dose of 2,600 mg/day (e.g., 2x650mg cap twice a day) for no more than 3 days/week. Combination products containing codeine, hydrocodone or oxycodone may be used on a p.r.n. basis only (not to exceed 5 consecutive days) and not within 24-hours before a clinic visit. Opioid analgesics are contraindicated as they have the ability to act as an NMDA antagonist.
Anesthetics • *General* • *Local*	 (N) (Y)	 (N) (N)	
Anorexics	(N)	(N)	
Anticholinergics	(N)	(N)	Includes Cogentin. Anticholinergics for bladder control are to be avoided if possible. When needed some, such as Detrol is allowed. Call Medical Monitor.
Anticoagulants	(N)	(Y)	Heparin is not allowed
Anticonvulsants	(N)	(N)	Divalproex, Valproate, Topiramate and gabapentin are prohibited. Anticonvulsants with

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Chronic Use	Restrictions
			no known significant cognitive effects, such as Lamictal, Pregabalin, Levetiracetam are allowed. Call the medical monitor for other anticonvulsants. Patient must have been on a stable dose for 3 months prior to screening.
Antidepressants	(N)	(Y)	MAO inhibitors, antidepressants with anticholinergic effects (e.g. tricyclics), and chronic use of sedating antidepressants (e.g. mirtazipine) are not allowed. Sedating antidepressants can be used sparingly at low dose, as needed for sleep; avoid using 12 hrs prior to efficacy assessments. Dose and medication must be stable for 1 month prior to Screening.
Antiemetics	(Y)	(N)	Antiemetics with sedative properties (e.g. first generation antihistaminics) are not allowed. Antiemetics such as phosphoric acid preparations (Emetrol, Emecheck), Pepto-Bismol, and cola syrup are allowed.
Antifungal agents • *Systemic* • *Topical*	 (N) (Y)	 (N) (Y)	
Antihistamines	(Y)	Call	Non-sedating antihistaminics such as Allegra (fexofenadine), Zyrtec (cetirizine) etc are allowed. Sedating antihistaminics are not allowed. See cough and cold preparations for combination products.
Anti-inflammatory drugs	(Y)	(Y)	Indomethacin and systemic corticosteroids are not allowed.
Anti-neoplastics	(N)	(Y)	Tamoxifen is allowed. Dose must be stable for 3 months prior to Screening.

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Chronic Use	Restrictions
Anti-obesity	(N)	(Y)	Xenical (orlistat) Cetilistat, Lorcaserin (Belviq) are allowed. Others such as Qsymia (a combination of phenermine and topiramate) are not allowed. Call Med Monitor. Dose must be stable for at least one month prior to Screening.
Anti-Parkinson's drugs	(N)	(N)	Includes dopaminergic agents, amantadine, selegiline, Cogentin, and MAO inhibitors.
Antipsychotics	(Y)	(Y)	Clozapine and antipsychotics with anticholinergic effects are not allowed. Limit use to low doses and only if absolutely needed. Call Medical Monitor. Doses must be stable for at least *one month* prior to Screening.
Anxiolytics	(Y)	(N)	Limited use of short/medium acting benzodiazepines if needed is allowe Do not use within 12 hrs before efficacy assessments.
Cholinesterase inhibitors	(N)	(Y)	Alzheimer's disease medications such as Aricept (donepezil) Exelon (rivastigmine), and Reminyl (galantamine) must be on a stable dose for at least 3 months prior to Screening. Usage must continue unchanged throughout the study.
Cough/Cold preparations	(Y)	Call	Decongestants containing dextromethorphan or narcotics are not permitted. Preparations containing pseudoephedrine or phenylpropanolamine are not permitted. *See Antihistamines.*
Ginko biloba	(N)	(Y)	Dose must be stable for at least one month prior to Screening.
Hormones	(N)	(Y)	Medication and dose must be stable for 3 months prior to Screening.

Drugs Allowed (Y) and Not Allowed (N) as Concomitant medications in this study.

Drug Class	Usage (p.r.n.)	Chronic Use	Restrictions
Hormone suppressants	(N)	(Y)	Proscar (finasteride) is allowed. Dose must be stable for 3 months prior to Screening.
Hypoglycemic agents	(N)	(Y)	Oral hypoglycemic agents and insulin are allowed. Dose must be stable for 3 months prior to Screening.
Hypolipidemics	(N)	(Y)	Statins are allowed. Dose must be stable for at least one month prior to Screening.
Insulin	(N)	(Y)	Patients must be well controlled and stable.
Laxatives	(Y)	(Y)	Fiber-based products and Colace (docusate sodium) are allowed.
Muscle relaxants	(N)	(N)	
Psychotropic drugs not otherwise specified (including herbal products)	(N)	(N)	Call medical monitor
Sedatives/hypnotics	(Y)	(Y)	Zolpidem, zaleplon, trazodone, chloral hydrate, mirtazapine, and the occasional use of benzodiazepines for sleep is allowed. Where possible, these should not be used within 12 hrs prior to efficacy tests.
Steroids • *Systemic* • *Topical* • *Inhalant*	 (N) (Y) (Y)	 (N) (Y) (Y)	
Stimulants	(N)	(N)	Includes Ritalin, Concerta, any methylphenidate preparations, Cylert (pemoline), etc.
Tocopherol (Vitamin E)	(N)	(Y)	Dose more than 400 IU per day not allowed; Dose must be stable for at least one month prior to Screening.
Vaccines for AD	N	N	Patients treated with active vaccine against amyloid/tau within 2 years are not allowed.

15 APPENDIX 2 LIST OF REFERENCES

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16 APPENDIX 3 SUMMARY OF CHANGES

16.1 Protocol Version 2.0 June 1, 2020

General global edits:

Several corrections and clarifications were made to address discrepancies in the text. Key changes are noted below.

Synopsis and relevant sections:

- The version and date were updated.
- Subjects will be stratified by baseline SIB total scores, which will be balanced between treatment groups.
- The anticipated start and stop dates were updated to reflect the delays resulting from the widespread COVID-19 pandemic. These dates are only estimates at this time, pending further evaluation of the potential impact on subject participation.
- The number of subjects has been modified from 46 to 100.

- All subjects will proceed to a second course of treatment, 7 doses beginning at Week 15.
- The primary endpoint is at Week 28, after 2 courses of treatment have been administered.
- The final follow-up visit will be at week 30.
- The Schedule of Activities has been revised to illustrate the new visit schedule and procedures to be performed.

Protocol sections 4.0 and 9.0:

Revisions were made to be consistent with the planned statistical analysis. For the primary endpoint analysis, the test of the null hypothesis will be a superiority test based the treatment difference in Week 13 SIB from baseline means as assessed by general estimating equations (GEE) regression models. Secondary and exploratory endpoints will be similarly assessed.

Section 6.1.1:

The option to utilize a Pre-Screening Consent Form was added. The purpose of the Pre-Screening Consent is to allow access to medical records prior to a subject's onsite screening visit. Use of this consent will reduce the occurrence of onsite screening visits by subjects ineligible for the study based on medical history. No study procedures will be performed under this preliminary consent.

16.2 Protocol Version 3.0 June 30, 2020

Synopsis and Section 4.4.1:

Inclusion criterion #5 has been revised. Patients must have a baseline SIB total score of at least 60 and may not have a SIB score >93 at screening. Previous versions of the protocol required only that subjects be able to complete at least one item on the SIB, but for the moderately severe AD subjects eligible for this study, a range of scores between 60 and 93 is appropriate.

Section 6.1.21 added: Early Treatment Discontinuation and Follow-up

If for any reason, the investigator, subject or caregiver decide at Week 13 that further study drug treatments should not be administered, the subject will not enter Treatment Period 2, but will be encouraged to continue follow-up visits. The visits will take place at Weeks 15, 20, 24, and 30. All procedures listed for these visits should be performed, with the exception of study drug infusion, infusion-related vitals, and ECG. Subjects who discontinue treatment are not eligible to resume treatment. Subjects may discontinue follow-up at any time after Week 15, the 30-day follow-up visit for Treatment Period 1.

16.3 Protocol Version 4.0 June 7, 2021

General global edits:

Several corrections and clarifications were made to address discrepancies in the text. Key changes are noted below.

- The version and date were updated.
- The name change of the sponsor from Neurotrope to Synaptogenix has been reflected in the text.

Synopsis:

The medical monitor's name and contact information have been updated.

Synopsis and Section 9.5:

The secondary analyses has been changed, removing analyses of SIB total scores at Weeks 5 and 15 and adding an analysis at Week 30.

Synopsis and Section 4.4.2, Exclusion Criterion 9:

> Restriction of the use of acetaminophen has been revised to allow no more than 2,600 mg/day of acetaminophen for more than 3 consecutive days within 14 days prior to screening.

Synopsis and Section 9.1:

The per protocol analysis set has been further defined. To be included, subjects must have received at least 11 of the14 doses (80%).

Section 2.1.1.3:

ClinicalTrials.gov study identifier for study NTRP101-203, NCT03560245, has been provided to facilitate review of adverse events that occurred in that study.

Section 2.1.2.3:

ClinicalTrials.gov study identifier for study NTRP101-202, NCT02431468, has been provided to facilitate review of adverse events that occurred in that study.

Sections 6.0.1.1 and 6.1.1:

B12 testing has been removed for follow-up of abnormal TSH at screening.

Section 6.1.22 has been added to describe procedures for early treatment discontinuation follow-up.

Section 9.4:

Text was added to address handling of early study drop-outs. Patients who drop out of the study prior to the first efficacy assessment will be replaced.

Section 14, Appendix 1:

Restricted concomitant medications have been revised as follows:

- Prn administration of acetaminophen for pain may be used with a maximum dose of 2,600 mg/day (e.g., 2x650mg cap twice a day) for no more than 3 days/week.

- Antacids, antianginal medications, antiarrhythmics, antiasthma agents, antibiotics, antidiarrheal preparations, antihypertensives, antiviral agents, BPH agents, diuretics, and H_2 blockers have been removed from the list.

16.4 Protocol Version 5.0 December 20, 2021

Global changes: The protocol version and date have been updated.

The protocol previously stated that blood samples will be drawn to measure the presence or absence of bryostatin after the initial dose of study drug on Day 0, and again after dosing on Day 105. However, the specialized laboratory where the testing was to be done has been unable to perform the test with adequate sensitivity. We have been given approval by the NIH, which is a sponsor of the study, to remove the test. The test is not included in any of the planned safety or efficacy analyses. For this reason, it is no longer necessary to draw blood samples at these two timepoints. The text affected by this revision are in Section 6, Table 1, Schedule of Activities, Section 6.0.1.1, Laboratory, Section 6.1.2, Week 0, and Section 6.1.11, Week 15.

The previous version of the protocol stated that patients who discontinue the study prior to the first efficacy assessment (Week 5, Day 35) will be replaced. The protocol has been revised to allow one additional patient to be added to the study for each patient who discontinues prior to the primary endpoint (Week 28, Day 196). Revised text in Section 9.4 as well as the synopsis reflect this change.

Section 9.4 has been revised to add Week 30 SIB scores to the data to be used in the regression models, and to state that both linear and non-linear terms will be considered in the regression models to be employed in analyses. Details will be provided in the statistical analysis plan.

16.5 Protocol Version 6.0 September 1, 2022

The protocol previously included a follow-up visit at Week 42. The Week 42 visit has been removed. However, data collected at this visit for subjects who completed the visit prior to implementation of this amendment will be included in the analyses as described.

References to PKCε testing and analysis have been removed, since no PKCε samples were collected for this trial.