Protocol Number HT 02-121: A Phase 2 Safety Study of L1-79 for the Treatment of Autism

NCT02947048

Amendment to HT 02-121 dated 23 January 2018 and protocol dated 10 March 2017

Amendment to Protocol Number: HT 02-121 (Version Number 49 Dated 10 March 2017)

A Phase 2 Safety Study of L1-79 for the Treatment of Autism

Summary of Changes to Protocol Number: HT 02-121, Version Number 49 Dated 10 March 2017 to Protocol Amendment Dated 23 January 2018:

The purpose of this protocol amendment is to update the sponsor information for this study. The new sponsor for this study is:

Yamo Pharmaceuticals
c/o Columbus Nova
900 Third Avenue, 19th Floor
New York, NY 10022

There are no other changes to the study protocol.

Sponsor Signatories:

INVESTIGATOR AGREEMENT PAGE FOR PROTOCOL AMENDMENT DATED 23 JANUARY 2018

I have read the protocol amendment for Study HT 02-121 entitled "A Phase 2 Safety Study of L1-79 in the Treatment of Autism". I will conduct this in compliance with the study protocol, Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines, and all applicable regulatory requirements, and will complete the study within the time designated.

I will provide copies of the protocol amendment and all information on the study drug relating to pre-clinical and prior clinical experience that are furnished to me by the Sponsor to all physicians, nurses and other personnel responsible to me who participate in this study and will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I agree that the conduct and results of this study will be kept confidential. I agree that the case report forms and other data pertinent to this study are property of the study sponsor who may utilize the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of multi-center study, if applicable. I further agree that Yamo Pharmaceuticals shall have access to any source documents from which case report form information may have been generated.

I will submit this protocol amendment to my IRB for approval.

_____

Signature

_____	_____	_____
Name	Date	Title

Investigational New Drug Protocol

Protocol Number: HT 02-121

A Phase 2 Safety Study of L1-79 for the Treatment of Autism

Sponsor:

Dr. Peter Halas

CONFIDENTIAL DOCUMENT

Version Number
49

Revised: March 10, 2017

Dr Peter Halas

Investigational New Drug Protocol

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RESTRICTED DISTRIBUTION OF PROTOCOLS

- This protocol contains information that is confidential and proprietary. The information contained herein is provided for the purpose of conducting a clinical trial in collaboration with Dr. Peter Halas.
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- The contents of this protocol may be disclosed to study personnel under your supervision and to your Institutional Review Board(s). The contents of this protocol may not be disclosed to any other parties (unless such disclosure is requested by Dr. Halas).

PROTOCOL SYNOPSIS

- Study Drug: L1-79

- Protocol Number: HT 02-121

Protocol Title: A Phase 2 Safety Study of L1-79 in the Treatment of Autism

- Study Phase: 2

- **Study Design:** This study has a dose escalating cohort design. Treatment arms consist of L1-79 at doses of 100 mg t.i.d (or placebo), or 200 mg t.i.d., (or placebo). Pharmacokinetics will be assessed in initial cohorts of 5 patients for each dose group followed by a double blinded, placebo-controlled assessment of PK/PD and safety in a cohort of 15 patients randomized 2:1 active to placebo. Groups 1& 2 below can start simultaneously. While the FDA is reviewing the data from Group 1, Groups 2 and the placebo patients randomized with Group 2 will be ongoing. All 5 subjects assigned to Group 1 (100 mg L1-79) must have completed the PK portion of the study with results analyzed and accepted by the FDA before subjects in Groups 3-5 can begin treatment.

- Sample Size: N=40
    - Group 1 (n=5) 100 mg L1-79 (1x100mg capsule+1 placebo capsule)
    - Group 2 (n=10) 100mg L1-79 (1x100mg capsule+1 placebo capsule)
    - Group 3 (n=5) 200 mg L1-79 (2x100 mg capsules)
    - Group 4 (n=10) 200 mg L1-79 (2x100 mg capsules)
    - Group 5 (n=10) Placebo (2 placebo capsules)

  All Groups will receive the assigned study drug three-times daily.

- **Study Population:** Male subjects with autism between the ages of 13 and 21 years of age who meet the entry criteria and who are able to complete standardized measures allowing them to participate in this study.

- **Major Inclusion Criteria:** Males between 13 and 21 years of age, signed informed consent, normal clinical laboratory values, DSM-5 compliant diagnosis of autism spectrum disorder, confirmed by the Autistic Diagnosis Interview Review (ADIR), and by the Autism Diagnosis Observation Schedule (ADOS) score consistent with a diagnosis of autism, no more than one concomitant medication, on a stable regimen for at least 2 weeks prior to enrollment and no planned changes in psychosocial interventions during the trial.

- **Major Exclusion Criteria:** Any co-morbidities, including Fragile-X syndrome, epilepsy, Retts syndrome, ADHD, or other disease or syndrome aside from autism that requires treatment. Any other psychiatric disorder, or out of range lab values. DSM-5 diagnosis of schizophrenia, schizoaffective disorder, alcohol use disorder; active medical problems: unstable seizures (>2 in past month), significant physical illness.

  - **Experimental Treatment:** L1-79 at doses of 100, or 200 mg, or placebo 3 times daily for 4 weeks.

  - **Non-Experimental Treatment**: Placebo.

  - **Dosage and Administration:** L1-79 or placebo, as assigned or as randomized, will be administered orally according to the regimen above.

  - **Evaluation Schedule:** Subjects will be evaluated within one week prior to study accession, and weekly throughout the dosing period, and again 4 weeks after the cessation of treatment. The Assigned Dosage Groups (Groups 1 and 3) will have PK blood draws and EKG the randomized group will not have.

  - **Safety Measures:** All Groups will have regularly scheduled complete history and physical examination that includes orthostatic blood pressure measurements, vital signs, CBC, differential, platelet counts, urine analysis, serum analytes including: total protein, albumin, glucose, BUN, creatinine, direct and total bilirubin, alkaline phosphatase, phosphorous, calcium, AST, ALT, sodium, potassium, chloride, bicarbonate, T_4, TSH, and adverse events assessments. The Assigned Groups (1 and 3) will also have electrocardiograms taken at the study screening visit and at the week 1.

  - **Total Study Duration:** It is expected that the entire study from screening of the first patient until the last patient enrolled has completed the last visit to require a total of 36 weeks. This period was estimated to include an 8 weeks recruitment, 8 weeks for screening, and 8 weeks' for treatment of all patients enrolled in the study and 8 weeks for follow-up.

  - **Study Endpoints:** The primary end point will be an assessment of the safety of L1-79 based upon reported adverse events and changes in baseline in physical examination parameters that include orthostatic blood pressure, clinical laboratory measures, and ECGs. Secondary endpoints will include an assessment of pharmacokinetics and pharmacodynamics, as well as the attending physicians assessment as quantified by the Clinical Global Impressions scale based upon

changes from baseline in various psychometric tests, including the Vineland Adaptive Behavior Scale 2nd edition (VABS II, VABS) questionnaire, the Autism Diagnostic Observation Schedule (ADOS), the Aberrant Behavior Checklist-Community (ABC-C), the Spence Anxiety Scale (SAS), the Repetitive Behavior Score – Revised (RBS-R), the Social Responsiveness Scale (SRS), as well as from their personal observations in the clinic, and anecdotally as provided by parents or caregivers over the course of this study.

1.0 INTRODUCTION AND RATIONALE

L1-79 is being developed for the treatment of autism. Dr. F Peter Halas holds IND 128673 and is also one of the Principal Investigators. Yamo Pharmaceuticals LLC, a part of Hoffman Technologies is providing support and L1-79 for the study.

L1-79 is racemic α-methyl-para-tyrosine (AMPT). This molecule was developed by Merck in the 1950's & 60's. The L-isomer was approved in 1979 as a presurgical treatment for the excision of pheochromocytoma tumors under the tradename Demser®. Because pheochromocytomas produce high levels of catecholamines, surgical manipulation of these masses liberates substantial concentrations of epinephrine and norepinephrine resulting in adverse cardiovascular events. Demser inhibits the first, and rate limiting, step in catecholamine synthesis, the conversion of tyrosine to dihydroxyphenylalanine (DOPA), and thus reduces the synthesis of dopamine (DA), norepinephrine (NE), and epinephrine (E). This inhibition has the effect of reducing tissue catecholamine levels making the tumor more amenable to extirpation without adverse consequences. Demser has also been approved for the treatment of subjects with pheochromocytoma for whom surgical excision is not an option to reduce the cardiovascular consequences of elevated levels of circulating catecholamines.

Catecholaminergic functions in the CNS and in the gut have been implicated as underlying the symptoms of autism. In the brain, dopaminergic systems have been shown to underlie systems that mediate pleasure, irritability, agitation, reward, and other symptoms that characterize autism. In the gut and mesentery, catecholaminergic systems are known to modulate digestion, and may underlie the digestive and dietary abnormalities associated with autism.

L1-79 has been used in a 30 patient phase 1 trial as one agent in the polytherapy named SM-88 (previously called SMK) (J Clin Oncol 31, 2013 suppl; abstr e22095). L1-79 was used at a dosage of 280 mg/d, along with daily 3-Amino-2-hydroxy-4-phenylbuteryl]-L-leucine (55 μg/d), phenytoin (32 mg/d), melanin (50 μg/d), and the melanin inducer melanotan II (10 μg/d) (IND #127977). In this regimen, L1-79 was administered to stage 4 metastatic cancer patients with a variety of tumor types including breast, prostate, pancreas, colon, lung, appendix, and others, who had failed all available therapeutic regimens.

An exploratory study intended to observe the effects of L1-79, when administered to patients with autism spectrum disease, was initiated at two sites in New Jersey. L1-79 was given to 10 patients to date on a t.i.d. schedule. Preliminary results indicated that L1-79 reduced the core deficits in a number of subjects, with the racemic form of the drug being more effective than either of the two stereoisomers alone. Utilizing the Aberrant Behavior Checklist – Community (ABC-C), Autism Diagnostic Observation Scale (ADOS), and Connor Parent Rating Scale (CPRS), improvements in all of the core symptoms of autism have been observed to occur quickly in subjects of both sexes and

ranging in age from 2½ to 24 years of age, with continual improvement with treatment over time.

Most of the clinical experience with L1-79 for the treatment of autism is with doses of 100-300 mg t.i.d.. This study seeks to quantify the safety and efficacy of L1-79 administered t.i.d. in doses of 100 or 200 mg to subjects with a diagnosis of autism based upon their ADOS results in a prospectively randomized and double-blind manner.

2.0 STUDY PURPOSE AND OBJECTIVES

2.1 Purpose

The purpose of this clinical trial study is to determine whether L1-79 is a well-tolerated and clinically useful agent for the treatment of ASD, and to assess the pharmacokinetics and pharmacodynamics of 4 weeks of t.i.d. dosing with L1-79.

2.2 Study Objectives

2.2.1 PRIMARY OBJECTIVE

To document the safety of L1-79 by assessing adverse events, electrocardiographic and physical examination measures, including vital signs and laboratory parameters at 2 different dose levels of L1-79.

2.2.2 SECONDARY OBJECTIVES

To document the PK and PD of L1-79 in a repeated dosing clinical situation, and to assess any change from baseline in the core symptoms of autism and associated behaviors using various standardized, validated ASD assessment instruments, and by comparing the results of subjects randomized to receive 1 of 3 different dosage levels of l-79 against placebo in a double-blind fashion. Also, changes in the ADOS core, including the severity scale, and the Clinical Global Impressions scale (CGI), including severity and improvement subscales will be assessed.

3.0 DESIGN AND METHODS

3.1 Study Design

This is a five-arm design that incorporates 2 open label groups whose doses are known for the purpose of understanding PK/PD and to determine if there are any EKG changes associated with the administration of L1-79, and a 3-group prospectively randomized, double-blind, trial of L1-79 at 2 dosage levels versus placebo.

Two dosages of L1-79 will be tested in this study: 100 mg t.i.d. and 200 mg t.i.d. The investigators in this study have the most experience with these two dosages during exploratory use of L1-79 described above. In preliminary observations in a number of patients between the ages of 2.75 and 24 years of age doses between 90 to 400 mg t.i.d. were well tolerated, and no evidence was found that suggests a need for weight based dosing. These findings were presented to the FDA.

The first cohort of 20 patients to be enrolled will all receive L1-79 100 mg t.i.d., and will be comprised of 3 groups of patients. The first 100 mg group will differ from the others in that they will get blood samples drawn for PK analysis and EKGs will be taken. The safety and PK data from this group will be submitted for FDA review and acceptance before the 200 mg t.i.d. cohort will be enrolled. The remaining 15 patients in this cohort will be randomized to receive either L1-79 100 mg t.i.d. or placebo on a 2:1 basis (2 L1-79 patients for each placebo patient). While the FDA is reviewing the data from the first 5 patients all 100 mg t.i.d. patients will continue to be treated.

The second cohort is identical to the first. The initial 5 patients to be enrolled will differ from the others in that they will get blood samples drawn for PK analysis and EKGs will be taken. The safety and PK data from this group will be submitted for FDA review and acceptance. The remaining 15 patients in this cohort will be randomized to receive either L1-79 200 mg t.i.d. or placebo on a 2:1 basis (2 L1-79 patients for each placebo patient). While the FDA is reviewing the data from the first 5 patients all enrolled patients will continue to be treated

Adolescents, between the ages of 13 and 21 years, with ASD who meet the entry/exclusion criteria, and with sufficiently high function to complete this study in the opinion of the Investigator, will be treated daily for 4 weeks. Standard psychometric tests will be utilized in the clinic and at home to ascertain affect and performance in order to assess changes in the symptoms and the diagnosis of autism.

Enrollment will be limited to male patients pending FDA approval and the completion of reproductive toxicology studies.

3.2 Study Endpoints

3.2.1 SAFETY ENDPOINTS

Safety is the primary endpoint and analysis will focus on the following endpoints at each time point from the start of dosing through the 4-week treatment and observation period, and at a 4-week follow-up visit:

- EKG
  - Patients in the Assigned Dosage Groups (1 and 3) will also have an EKG at baseline and within 3 days prior to the their visits as described in 5.1.2.
  - In the event any EKG abnormalities appear to result from treatment in the Assigned Dosage Group then additional EKG may be required as described in section 5.5.2
- Before and after the Active Treatment phase
  - Physical exam with vital signs, including orthostatic blood pressure
  - Hematology
  - Serum Chemistry
  - Urinalysis

- Active Visits, weeks 1-4
  - Vital signs findings, including orthostatic blood pressure,
  - Adverse Event (AE) reporting
  - Assessment of concomitant medications

3.2.2 EFFICACY ENDPOINTS

3.2.2.1 Main Efficacy Endpoints

- The primary efficacy endpoint will be the determination of clinical improvement by the Investigator as documented in the Clinical Global Improvement (CGI) scale and subscales (including severity and improvement) based upon his/her clinical observation and the results of the test scores as measured in the overall scores by the tests described below.

3.2.2.2 Additional Efficacy Endpoints

- Changes from baseline in the individual dimensions of the VABS questionnaire
- Changes from baseline in the VABS caregiver rating scale
- Changes from baseline in the ADOS scores and subscores
- Changes in the Clinical Global Impressions scale and subscales.
- Changes in the SAS
- Changes in the SRS
- Changes in the ABC-C scale and subscales
- Clinical opinions of observable changes from baseline.

3.2.3 PHARMACOKINETICS

The pharmacokinetics of L1-79 will be determined in the first week of treatment for the first 5 patients assigned to each Dose Arm (100 mg t.i.d. or 200 mg t.i.d.) The results of these analyses will be used to determine the exposure to L1-79 at the two proposed doses

3.3 Regulatory Compliance

This trial will be conducted in compliance with the study protocol. ICH and Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements will be adhered to by all personnel at all times.

3.4 Principal Investigator and Study Coordinator

It is the responsibility of the Investigator to execute this protocol as written in all details.

The Investigator will appoint a study coordinator with specific responsibilities for assuring that all of the elements of this protocol are conducted exactly as written. The study coordinator's responsibilities will include, but not be limited to:

- Scheduling the patient visits and assuring their timely presence
- Conducting those elements of the protocol assigned to the study staff by the Investigator (e.g., collection of vital signs, blood pressure, VABS II, ABC, caregiver forms, etc.)
- Assurance that all data are entered into the database within 3 days of the receipt of the data,
- Assuring that all data required by the sponsor are delivered to the sponsor in a timely manner.
- Training of study staff on the GCP guidelines and the details of this protocol, the methods and procedures by which this protocol is to be executed, and oversight over the execution of the protocol.

4.0 STUDY POPULATION

The study will enroll 40 subjects who meet the inclusion and exclusion criteria outlined below and who received at least one dose of the study medication.

Only males will be enrolled in this study due to the lack of nonclinical reproductive toxicology. Subjects will be randomized or assigned to each of the treatment groups described herein such that that 15 subjects are randomized to each L1-79 treatment arm at either 100 or 200 mg t.i.d., and 10 subjects will be randomized to t.i.d. placebo

4.1 Inclusion Criteria

- Subjects or their care givers willing to sign informed consent or to have informed consent provided by their legal guardians or proxies. (Appendix B). All subjects <18 years old or those unable to care for themselves must have the caregiver's consent.
- Subjects must be between the ages of 13 and 21 years of age
- Subjects must be male
- Subjects must be willing and able to participate in the testing procedures sufficient to obtain valid scores on the tests used herein.
- Must be stable on no more than one concomitant medication, and no planned changes in psychosocial interventions during the trial
- Subjects in the Assigned Dosage Groups must be tolerant of blood draws and electrocardiograms
- Diagnosis of ASD based upon the DSM-5 criteria and confirmed with the ADI-R and ADOS test that confirms a diagnosis of autism, and expert clinical opinion (Appendix F).
- Subjects must, in the opinion of the Investigator, be sufficiently tolerant and capable of complying with the requirements of this trial. For example, patients who will not tolerate blood draws or EKG are not qualified candidates for this study.
- Signed study compliance agreement (Appendix D) by the patient or caregiver
- As the Assigned Dosage Group will have repeated blood draws and EKG the investigator must be satisfied that the first 5 patients assigned to each dosage group are willing and able to comply with this regimen

4.2 Exclusion Criteria

- Sexually active males
- Fragile-X syndrome, Rett syndrome, or other co-morbidity including, but not limited to, cancer, asthma, genetic disease, or any disease or syndrome that requires drug therapy.
- DSM-5 diagnosis of schizophrenia, schizoaffective disorder, alcohol use disorder or ADHD
- Active epilepsy
- Out of range hepatic or renal function tests

- Presence of any active medical problem (e.g., unstable seizure disorder or heart disease)
- Any unexplained laboratory value
- Subjects requiring more than 1 medication for the treatment of autism, or who have not been weaned to their lowest tolerable dose of medication
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic cardio-vascular disease, hepatic disease, renal disease, skeleto-muscular disease, HIV, HCVA, HBV, or psychiatric illness/social situations that would limit compliance with study requirements.
- Any disease that requires chronic treatment.
- Any disease that requires treatment with immunosuppressive drugs
- Current or lifetime diagnosis of severe psychiatric disorder (e.g., bipolar disorder, etc.);

4.3 Group Sizes

The study includes a total of 40 patients equally allocated to 2 placebo controlled treatment arms (100 mg or 200 mg L1-79 t.i.d. The first 5 patients in each Treatment Arm enrolled and will be required to provide EKG tracings and blood specimen(s) for determination of pharmacokinetics for the estimation of exposure. Once this lead-in group has completed one-week of treatment and EKG tracings are not abnormal and blood specimen(s) for the determination of L1-79 concentrations have been analyzed, and a report on the PK and safety data from this group has been reviewed by the FDA and permission from the FDA is obtained to escalate the dose, then, 20 additional patients will be enrolled and treated in the same manner as the 100 mg t.i.d. group, such that 5 open label patients will be treated as described above and 15 patients will be randomized 2:1 to receive 200 mg L1-79 t.i.d.

5.0 STUDY PROCEDURES

5.1 Consent and Assignment of Subjects to Treatment

Each patient or their representative must sign a copy of the informed consent document. The patient will be asked to provide assent to participate in the study (Appendix B). The study staff will explain this form in non-technical language, in detail, and will answer all questions that a patient might ask. Staff will explain to all subjects that subjects who qualify for entry into this trial will receive an experimental treatment which they must take daily as instructed and must come back to the clinic for regularly scheduled visits.

The patient, or caregiver of each patient will sign the Study Compliance Agreement (Appendix D) in which they agree to administer the test medication as instructed by their attending physician in compliance with this protocol. Further, this agreement stipulates that the caregiver of each patient will complete their obligations under this protocol as instructed by the Investigator and his/her staff; including visit attendance, test form completion, reporting of adverse events, and so forth. Additionally, this agreement requests, but does not require, that caregivers provide any *ad hoc* comments regarding the behavior of the patient or their responses to treatment be forwarded weekly to the Investigator to document changes in the patient's condition at home and to add any notes to the database that are appropriate to understanding the response of the patient to treatment.

After satisfying entry criteria and giving signed informed consent and agree to the compliance document, subjects will be enrolled in the trial

5.1.1 ASSIGNMENT OF PATIENTS TO GROUPS

At each of the two tested dosage levels, the first 5 patients in each group will be assigned to receive the specified dose of either 100 mg t.i.d. or 200 mg t.i.d., whereas the following 15 patients in that group will be randomized to receive the specified dosage or placebo. After being assigned to a treatment arm each patient will be assigned a study number comprised of a 2-digit site identifier and a 3-digit patient identifier.

No patient will receive more than 100 mg t.i.d until permission to escalate to 200 mg t.i.d. is obtained from the FDA after their review of the first week of safety and PK data from the 100 mg group. This permission will follow if the safety data submitted for the first week of dosing in the Assigned Dosage Group is assessed by the FDA to be sufficiently safe to allow for a dosage escalation.

Each study site will be identified by a 2-digit number beginning with 01. Each patient screened for admission into the study will be assigned a unique sequential number that also identifies their study site. Thus, the 1st patient enrolled in the first study site will be patient 01-001 and the 2nd patient enrolled at the 2nd study site will be patient 02-002.

Study numbers will not be assigned until a patient is qualified and entered into the trial. Screening failures will not be assigned numbers. However, a list of screen failures and their demographic data will be maintained by the Investigator.

Patients will be enrolled and receive their first dose within 3 weeks of completing the screening procedure.

5.1.2 ASSIGNED DOSAGE GROUPS

The first 5 patients in each dosage group will be assigned to receive the active medication in an open label fashion. These groups will be treated identically to the Randomized group with 4 exceptions:

- Patients in this group will have blood samples drawn at baseline before and 1h after dosing, and at each active treatment visit 1h after dosing to determine their blood levels of L1-79 for pharmacokinetic and pharmacodynamics analysis.
- Patients in this group will have EKG taken at baseline and within 3 days prior to the Week 1, 2, 3, and 4 treatment interval visits as well as at the 1 week and 4 week post dosing follow-up visits. Patients in this group will have vital signs, physical exam, and ASD assessments will be performed, including: ABC, SRS, RBS-R, CGI-S, and CGI-I be assessed at 1-week post-dosing Patients in this group will have blood and urine samples drawn at baseline at baseline before dosing, at week 1, 2, and 3 active treatment visit 1h after dosing, and at the 1 week post dosing follow up for safety analysis.

Following the Week 1 visit for these patients and the completion of all assays for samples taken at the Week 1 visit, a report will be submitted to the FDA on the results from these patients. A second report on the results of these patients will be sent to the FDA following the final 1-week post-dosing visit for this group of patients.

5.1.3 RANDOMIZED GROUP

Following the enrollment of 5 open label patients as described in the Assigned Dosage Groups, an additional 15 patients at each dose level will be randomized 2:1 to receive either active drug or placebo (2 active to each placebo patient. These patients will be treated identically to those in the Assigned Dosage Groups with 3 exceptions:

1. No pharmacokinetic samples will be drawn,
2. No EKG will be performed
3. They will not have the 1 week follow-up, just the 1 month follow up.

After being randomized to a treatment arm each patient will be assigned a study number comprised of a 2-digit site identifier and a 3-digit patient identifier as described above.

Study numbers will not be assigned until a patient is qualified and entered into the trial. Screening failures will not be assigned numbers. However, a list of screen failures and their demographic data will be maintained by the Investigator.

Patients will be enrolled and receive their first dose within 3 weeks of completing the screening procedure.

5.1.4 PLACEBO ROLLOVER TO ACTIVE

- If the Investigator in collaboration with Yamo Pharmaceuticals (the manufacturer of the drug) believes that the L1-79 is sufficiently well tolerated and clinically useful to warrant continued treatment, then patients receiving placebo will be eligible for a 4 week course of treatment with L1-79 as outlined for the other patients treated with active drug in this protocol. At the present time, the permitted course of therapy does not extend past 4 weeks.
- The random code will only be broken after the last patient in a group has completed the last scheduled follow-up visit.
- Placebo treated patients who qualify for active treatment in a rollover fashion, and who desire to do so, will be indicated in the eCRF as has having affirmatively requested active treatment under the protocol. They will then qualify for extended treatment with active medication under the existing protocol and new, active, medication will be assigned to them on an open label basis at the same dose as their group had been receiving.
- Placebo rollover patients will be seen at 3 scheduled visits plus a follow-up visit as described in Appendix B.
    - There will be no Screening, as patients have already been screened
    - Rollover patients will not have any PK tests conducted
    - Baseline Visit
        - No randomization is required.
        - Roll over patients will get a physical (including vital signs)
        - Blood and urine samples will be taken for hematology, urinalysis and serum chemistry assessments.
        - No retained samples to be collected
        - All psychometric assessments described in Appendix A for the baseline visit will be taken
        - The initial 2 weeks of doses of active medication will be dispensed.
    - Week 2
        - A physical examination will be performed and the parents interviewed as to their observations regarding the effects of treatment over the past two weeks, and the final two weeks of active medication doses will be dispensed.
        - Patients will get a physical (including vital signs)

- No blood or urine samples will be taken
- No psychometric tests will be conducted at this visit.

- Week 4
  - The final active treatment assessment will be made, which will include a physical examination,
  - All blood and urine analysis described previously
  - No retained samples to be collected
  - All psychometric tests described for the 4 week visit in Appendix A.
  - Patients will get a physical (including vital signs)
  - A week 4 ADOS will be taken
- 4 weeks post treatment follow-up
  - The final assessment will be made, which will include a physical examination,
  - All blood and urine analysis described previously
  - Patients will get a physical (including vital signs)
  - No retained samples to be collected
  - All psychometric tests described for the 4 week visit in Appendix A.

5.1.5 EMERGENCY BREAKING OF THE RANDOM CODE

In the event a patient has an emergency that requires knowing which regimen he was receiving in this trial, that information can be obtained by calling (908) 310-7912 or (908) 236-9513. This number is for the use of the Investigator or other treating physician whose knowledge of the randomization is critical to the treatment of the patient.

5.2 Drug Administration

5.2.1 THE L1-79 REGIMEN

Subjects will receive either 100 mg or 200 mg or matching placebo t.i.d. for a total of 28 days of dosing. The doses of L1-79 were determined based upon preliminary clinical research in subjects between 2½ and 24 years of age and doses between 90 and 200 mg t.i.d..

5.2.2 THE PLACEBO REGIMEN

The matching placebo regimen consists of inert ingredients matched in taste, weight and appearance to the active drug and administered orally t.i.d. for 28 days.

5.2.3 DOSING INSTRUCTIONS

The study medication will be dispensed in containers that contain sufficient study drug for two weeks of t.i.d. dosing, plus 2 additional doses to be used if needed (44 doses) at the Day 0 and Week 2 visits. In order to maintain the double-blind, each dose will be

comprised of 2 capsules as described below. Thus, each biweekly drug allotment will consist of 44 packages of 2 capsules each sufficient for 3 daily doses times 14 days plus 2 extra doses to be used in the event that a dose or two is lost. Subjects will be instructed to take a dose (2 capsules) in the morning upon arising, afternoon at approximately 4 pm, and just prior to bed time. Capsules can be taken orally, or their contents can be mixed with food or drink as deemed necessary by the caregiver to facilitate the administration of the medication. Care will be taken to assure that 8 oz of water are given at the time of dosing to maintain hydration. For subjects unable to swallow capsules the may take the drug in food or drink. Patients should also be cautioned about potential sedative effects and instructed not to conduct activities like driving, which require alertness.

5.2.3.1 First Dose Safety Observation

The first dose of L1-79 in every patient will be administered at the study site, and each patient will be observed for a minimum of 2 hours post-dosing in order to assess adverse events. Special attention should be paid to potential AE known to be associated with impaired catecholaminergic function such as dystonias, cardiovascular events, extrapyramidal symptoms, and so forth.

5.3 Potential Side Effects and Treatment

The levo form of L1-79 (L-AMPT) is marketed under the name of Demser for the presurgical treatment of pheochromocytoma. Demser is prescribed for adults and children over 12 at doses between 1-4 g/d, with the lowest label dose of Demser being 250 mg qid. This is higher than the highest dosage used in this study. L1-79 is a racemate it contains the dextro form of the amino acid isomer and only 50% of the active Demser ingredient as determined by measuring the optical rotation. L1-79 has been tested in rodents and dogs and found to be well tolerated at multiples of the dose to be used in this trial. Based upon 4 week toxicological reports in rats and dogs a sufficient toxicology profile has been elaborated to support the use of L1-79 in a 4-week study in humans.

At the approved doses of ≥2g/d Demser may be associated with crystalluria, sedation, and other effects reported to have been mild. Mild depression and difficulties in sleeping have also been reported at these higher doses. These effects were observed to be transient. Investigators should instruct subjects and caregivers to maintain patient hydration, and to be aware of potential sedative effects that would limit the use of the drug when using power equipment or driving. It should be noted that the highest dose in this trial is equivalent to 300 mg of Demser daily, or 15% of the 2 g/d dose.

5.4 Concomitant Medication

Patients are permitted only 1 concomitant medication in this trial. Patients should be assessed for concomitant medications during the screening process and weaned down to the lowest possible effective level for the duration of this trial, including all follow-up visits.

5.5 Clinical and Laboratory Procedures

Prior to starting any procedure associated with this study, the patient or caregiver must give written informed consent (Appendix C) to participate and agree to abide by the requirements of this study. Study personnel experienced with ASD patients and their families will take great care to explain in detail and in easy to understand terms the purpose, objectives, methods, tests, study schedule, and any other pertinent information that might influence the granting of consent to participate. Similarly, study staff will take great care to elicit and answer all questions that arise in the course of describing this trial and will answer all questions fully. A copy of the consent form will be maintained with the patient's records.

This study will use the local certified clinical laboratory associated with the Investigators practice. CLIA certification and normal values will be obtained by the Investigator and provided to the Sponsor for each clinical lab used, and normal values will be updated after each calibration cycle.

A schedule of events can be found in Appendix A.

5.5.1 Screening Evaluation for Inclusion/Exclusion Criteria

Criteria for inclusion and exclusion of potential study subjects are outlined in Sections 4.1 and 4.2. All potential study subjects must be evaluated for the presence of all inclusion criteria and the absence of all exclusion criteria before enrollment in this study.

5.5.1.1 Medical History

Background information will be recorded once for each patient during screening for this study. This information includes age, gender, race and medical history including concomitant diseases and conditions associated with organ systems and chronic infectious diseases, as well as a detailed family history to ascertain any heritability of autism, cognitive dysfunction, epileptic or other diseases associated with autism.

Caregivers will be questioned about the patient's prenatal history, possible exposure to pesticides or other toxins, pre-natal maternal inflammation, fetal alcohol syndrome, and drugs taken by the mother during prior to, during, and after pregnancy.

In addition to the usual medical history questions asked of patients with ASD, patients and caregivers will be queried about their use of alcohol sugars such as xylitol, mannitol, and the dental health of the study subjects.

5.5.1.2 Physical Examination

All subjects will have a complete physical examination including vital signs at screening and again at the 4-week post-dosing follow up visit. Height will be recorded once at screening. Weight will be recorded at each physical exam. Any change from screening physical examination that is clinically significant and noted during follow-up will be recorded in the patient's medical record and on the CRF. Additionally, a physical exam will be conducted on the Assigned Dosage Patients at their 1 Week Follow Up visit.

5.5.1.3 Vital Signs

Vital signs obtained for each patient include orthostatic blood pressure (systolic/diastolic), heart rate (radial pulse) and respiratory rate at screening and all scheduled clinic visits.

5.5.1.4 Blood Pressure

Blood pressure (bp) will be taken at every visit. Orthostatic blood pressure will be assessed by recording blood pressure while sitting and then while standing in the following manner:

- Patient will sit down for 5 minutes
- Measure blood pressure and pulse rate
- Have the patient stand
- Repeat blood pressure and pulse rate measurements after standing 1 and 3 minutes

A drop in bp of ≥20 mm Hg, or in diastolic bp of ≥10 mm Hg, or experiencing lightheadedness or dizziness is considered abnormal.

5.5.1.5 Electrocardiograms

- In order to assess any possible changes in electrocardiographic variables, an EKG will be taken and read as specified in section 5.5.2. A pediatric cardiologist will read all EKGs.

5.5.1.6 PK Assessment

- Blood samples will be taken at baseline both before and 1h after dosing, and at each of the 4 weekly active treatment visits 1h after dosing in the Assigned Dosage Group for the purpose of measuring serum levels of L1-79.

5.5.1.7 Concomitant Medications

As documented in the history and at the screening visit, no patient currently receiving polytherapy for autism will be enrolled in this trial. Any agent which is being prescribed for the treatment of ASD will be noted as such in the eCRF. Subjects identified for accrual into this trial will be weaned to the lowest dose of any prescribed psychotropic medication over the two to four weeks preceding their screening visit deemed effective by the Investigator.

All prescription and nonprescription medication taken by the patient from 14 days prior to screening and up to and including the final visit will be recorded in the medical record and on the eCRF. Any addition, deletion, or change in the dose of these medications must be recorded.

Because the mechanism of L1-79 is the inhibition of catecholamine synthesis, the potential exists for interactions with neurologically active, and other, drugs. Investigators will be diligent in observing potential drug interactions and should appropriately reduce the dose of any concomitant medication that is observed to be potentiated in the presence of L1-79.

5.5.1.8 Clinical Laboratory Safety Assessments

The following parameters will be measured for the Randomized Groups at screening, at week 4, and at the 4-week follow-up, and in addition for the Assigned Dosage Groups at each weekly visit and the 1 Week Follow up using the central laboratory provided:

- Urinalysis
  - Color
  - Clarity/turbidity
  - pH
  - Specific gravity
  - Glucose
  - Ketones
  - Nitrites
  - Bilirubin
  - Urobilirubin
  - Blood
  - Protein
  - RBC
  - WBC
  - Squamous epithelial cells
  - Casts
  - Crystals
  - Bacteria
  - Yeast
  - Fractionated urinary catecholamines
  - Vanillylmandelic acid
- Hematology
  - hemoglobin,
  - hematocrit,
  - platelet count,
  - RBC
  - WBC with differential
- Serum Chemistry
  - sodium,
  - potassium,
  - chloride,
  - BUN,
  - creatinine,
  - AST,
  - ALT,
  - GGT,
  - LDH,
  - CO_2/bicarbonate
  - total protein,
  - albumin,
  - calcium,

- phosphorous,
- alkaline phosphatase,
- total bilirubin (direct, indirect, total),
- cholesterol,
- triglyceride,
- amylase, lipase
- T_4 & TSH
- Fractionated Plasma Catecholamines
- Metanephrines, plasma free & fractionated.

5.5.1.9 Blood Draws for Subsequent Testing

- At the time of the sample collection for the analysis of serum chemistry 2 additional red top tubes of blood will be drawn, spun down to separate the cells, and the serum will be frozen and stored for subsequent analysis. Samples will be labeled with the subjects' initials, study number, date of visit, and identified as a pre- or post-treatment sample.
- Frozen serum samples will be stored at the site for up to 7 years and saved for analysis after which they will be destroyed. It is likely that these samples will be analyzed for catecholamine and lipid fractions in the future. However, the precise analysis has yet to be determined, and will be based upon future research results. Separate informed consent will be obtained prior to any future analysis of these specimens, however, all samples will be identified only by protocol and patient numbers. No other patient identifiers will be used.

5.5.1.10 Spense Anxiety Scale

- The Spense Anxiety Scale (SAS) will be administered at baseline and at the 4 week follow-up visit, and also at the 1 wk follow up visit for the assigned dosage groups.

5.5.2 EKG

EKG will be taken by an outside pediatric cardiologist.

- Patients who are screened and those who participate in this study will have appointments made for them by the Investigator or his study staff with the cardiologist associated with the study site.
- All required EKG appointments will be made upon the accrual of a patient into this trial and that information will be provided to the caregiver in writing.
- Detailed instructions will be provided to the caregiver regarding the directions to the cardiologist's office, contact information, times of the appointments, and it will be confirmed that these EKG appointments are an essential part of the study and all visits must be made at the scheduled times.
- The Investigator and/or the study staff will be responsible for obtaining the results of these EKG and entering them into the database prior to the next scheduled study visit.
- EKG will be taken as part of the baseline screening procedure for the Assigned Dosage Group patients (Groups 1 & 3).

- Patients in the Assigned Dosage Groups will have a repeat EKG taken within 3 days prior to the Week 1, 2, 3, and 4 treatment interval visits as well as at the 1 week 4 week post dosing follow-up visits.
- EKG will be taken as necessary in any patient who manifests a potential cardiovascular AE in response to L1-79 such as tachycardia or bradycardia.
- In the event that 2 or more cardiovascular AE are reported in a group additional EKG may be warranted and a determination will be made as to the proper course of action at that time.

5.6 Clinical Evaluation

The purpose of this study is to assess the safety and efficacy of L1-79 in the treatment of autism. To that end, certain clinical evaluations (including physical examination, vital signs, and laboratory tests as described above) will be performed during different scheduled clinic visits.

5.7 Psychometric Testing

The following assessment instruments will be used in this study:

- Vineland Adaptive Behavior Scale II (VABS II): Questionnaire (Sparrow, et al 2006)
- Aberrant Behavior Checklist and subscales: (Aman, MG & Singh, N. 1988)
- Clinical Global Impressions Scale, and subscales (Guy 1976)
- Autistic Diagnostic Observation Schedule (Western Psychological Services)
- Autism Diagnostic Interview – Revised (ADIR): Rutter et al 2003)
- Social Responsiveness Scale (SRS): (Constantino, J. 2007)
- Spense Anxiety Scale (SAS): (Spense, SH 1998)
- Repetitive Behavior Scale – Revised (RBS – R): (Lam, KS & Aman, MG 2007)

Additionally, clinical observations will be made regarding by the Investigator at each visit that should include factors such as:

- the subject's eye contact
- abnormal gestures
- response to having their name called
- ability to draw specified shapes
- interaction with toys or other objects

5.7.1 Testing at Scheduled Clinic Visits

The following events will occur at the scheduled clinic visits during the treatment phase of the protocol by the Investigator or the appointed study staff:

- Review of the submitted VABS II caregiver form,
- Conduct a physical (screening, visit 4, and follow up visits) and review the vital signs (all visits),
- Caregivers will be questioned about Adverse Events,
- If appropriate, medication will be returned or dispensed and the medication log completed.

- A CGI-I and CGI-S assessment will be made
- An ABC-C test will be completed
- A SRS form will be completed
- An RBS-R form will be completed
- Caregiver anecdotes will be solicited and recorded
- Patient interactions with Investigator and caregiver will be noted.

5.7.1.1 Pre- Post-Dosing testing

- An ADOS test will be administered as part of the screening procedure. The ADOS will be used as a secondary outcome measure and will be repeated just prior to the 4th weekly treatment visit.

5.8 Investigator Rating of Patient Response

The CGI-S (severity) form will be completed at on day 0, and at each weekly visit during the dosing phase of the study, and at the follow-up visit. The CGI-I (improvement) will be completed at each weekly treatment visit.

5.9 Schedule of Procedures

The evaluation schedule for the study is provided in Appendices A and B and described below.

5.9.1 ACCRUAL OF SUBJECTS INTO THE STUDY

Following an assessment of each patient for compliance with the inclusion and exclusion criteria described above, acceptable subjects will be enrolled in this study. The screening visit and all tests that are required at screening will be completed such that subjects will receive their first dose within 3 weeks of screening.

5.9.1.1 Entry into the study

- At the time all inclusion and exclusion criteria will have been evaluated and met, the patient will be accepted for enrollment. Patients will be assigned a study number and randomized to one of the four treatment groups. The initial two weeks of medication will be provided at the time of randomization.
- The caregiver for each patient will be given instructions as to their responsibilities and how to perform them, which includes:

5.9.1.2 Explanation of Caregivers Responsibilities

- The caregiver for each patient accepted into the study will have their responsibilities as detailed in the Study Compliance Agreement explained to them in detail. These responsibilities include:
  - To make sure the patient takes the assigned study medication according to the study schedule
  - To make sure the patient attends each clinic visit at the appropriate time
- To return all unused medication at the 2 and 4 week visits

5.9.1.3 Enrollment of Subjects (Day 0)

- Subjects who meet the inclusion and exclusion criteria for this study will be enrolled. They will be issued a study number based upon a random assignment of subjects to dosage groups in a blinded fashion using a code provided by the sponsor.
- For each screened patient a discrete file will be created.
- For screen failures, their files will contain the screening data that supports their failure to qualify for enrollment in the study.
- For patents that qualify for enrollment, their files will contain all documentation pertaining to that patient's participation in the study, including:
    - A fully executed consent form
    - An executed assent form
    - A fully executed caregiver compliance form
    - Copies of the patient history and all laboratory, physical, and electrocardiographic results,
    - Copies of all psychometric tests
    - Copies of all physician's notes on the patient's participation in the trial, including any information submitted by caregivers.
    - Any information provided by caregivers
- Consistent with GCP, study information will refer to subjects only by study number or initials. No subject names or other identifying information will be provided.

5.9.1.4 Off-Site Events

5.9.1.4.1 Electrocardiograms

All EKGs will be read by an independent pediatric cardiologist. An EKG will be as specified in section 5.5.2. The follow-up EKG must be taken within 1 week following the patient's last dose.

5.9.1.4.2 ADOS

ADOS testing will be performed by a certified ADOS test administrator immediately before the screening visit and immediately to the end of of the 4 weeks of active dosing. The follow-up ADOS must be taken within 1 week following the patient's last dose.

5.9.2 SCHEDULED CLINIC VISITS – ALL PATIENTS

A listing of all events to be performed at each visit is presented in Appendix A. All data will be recorded in the primary source documents and entered into the electronic database within 3 days of each patient visit.

5.9.2.1 Screening Visit

- Assessment of each patient for compliance with the inclusion and exclusion criteria described
- Demography and Medical History including blood-related family members
- Blood and urine samples for safety analysis
- Blood drawn for plasma for laboratory studies and for storage
- Physical Examination including vital signs
- ADOS test

- ADI-R administered by telephone
- All current medications will be recorded
- Once the patient has completed all screening assessments and all inclusion criteria have been met, the patient will be randomized

5.9.2.2 Day 0 Visit

- Subjects will be assigned a randomized study number from a list of study numbers based upon a blinded random assignment of subjects to dosage groups. This study number, consisting of a 2 digit site number and a 3 digit patient number (i.e. XX-YYY) will identify the patient and the drugs allotted to that patient.
- Vital signs
- ASD assessments will be performed, including: ABC, SAS, SRS, RBS-R, CGI-S, & VAB II questionnaire.
- Question caregiver or patient about the patient's week, including questions regarding any changes in home life activities, events at school, sleep, or other matters germane to an understanding of the patient's autistic presentation.
- Assigned Dosage Group patients will also have an EKG, PK and safety blood draws, & 24h urine sample taken prior to dosing, with an additional PK blood draw 1 hour post dosing
- Record concomitant medications
- Record all adverse events
- Dispense 2 weeks of medication

5.9.2.3 Week 1 Visit (Study Day 7)

- Vital signs
- ASD assessments will be performed, including: ABC, SRS, RBS-R, CGI-S, and CGI-I
- EKG, Blood and urine samples for PK analysis (Assigned Dosage Group patients only)
- Blood and urine samples for safety analysis (Assigned Dosage Group patients only)
- Question caregiver or patient about the patient's week, including questions regarding any changes in home life activities, events at school, sleep, or other matters germane to an understanding of the patient's autistic presentation.
- Confirmation of medication administration
- Record concomitant medications
- Record all adverse events

5.9.2.4 Week 2 Visit (Study Day 14)

- Investigators will solicit any adverse events from the patient and/or caregiver and assess
- Vital signs
  - EKG, Blood and urine samples for PK analysis (Assigned Dosage Group patients only)

  - Blood and urine samples for safety analysis (Assigned Dosage Group patients only)
  - assessments will be performed, including: ABC, SRS, RBS-R, CGI-S, and CGI-I
- Question caregiver or patient about the patient's week, including questions regarding any changes in home life activities, events at school, sleep, or other matters germane to an understanding of the patient's autistic presentation
- Dispense 2 weeks of medication
- Confirmation of medication administration and the collection, counting and logging of unused medicine.
- Record concomitant medications
- Record all adverse events

5.9.2.5 Week 3 Visit (Study Day 21)

- Vital signs
- EKG, Blood and urine samples for PK analysis (Assigned Dosage Group patients only)
- Blood and urine samples for safety analysis (Assigned Dosage Group patients only)
- ASD assessments will be performed, including: ABC, SRS, RBS-R, CGI-S, and CGI-I
- Question caregiver or patient about the patient's week, including questions regarding any changes in home life activities, events at school, sleep, or other matters germane to an understanding of the patient's autistic presentation.
- Confirmation of medication administration
- Record concomitant medications
- Record all adverse events

5.9.2.6 Week 4 Visit (Study Day 28)

- ADOS (all patients) – to be performed during the last week of dosing while patients are still on medication
- Investigators will solicit any adverse events from the patient and/or caregiver and assess
- vital signs
- EKG, Blood and urine samples for PK analysis (Assigned Dosage Group patients only)
- Blood and urine samples for safety analysis for all patients
- Blood drawn for plasma for laboratory studies and for storage
- ASD assessments will be performed, including: ABC, SRS, RBS-R, VABS, CGI-S and CGI-I
- Question caregiver or patient about the patient's week, including questions regarding any changes in home life activities, events at school, sleep, or other matters germane to an understanding of the patient's autistic
- Record concomitant medications
- Record all adverse events

- Confirmation of medication administration and the collection, counting and logging of unused medicine

5.9.2.7 Week 4-5 (Study days 28-35; within 1 week after last dosing)

- Week 1 follow up for Assigned Dosage Group patients only
    - EKG
    - Physical exam with vital signs
    - Hematology
    - Urinalysis
    - Serum chemistry
    - Blood draw for storage
    - ASD assessments will be performed, including: ABC, SRS, RBS-R, CGI-S SAS, VAB II, and CGI-I
    - Record all adverse events
    - Question caregiver or patient about the patient's week, including questions regarding any changes in home life activities, events at school, sleep, or other matters germane to an understanding of the patient's autistic
    - Record concomitant medications

5.9.2.8 Week 8 Follow-Up Visit (Study Day 56)

All patients are to receive:

- Physical exam with vital signs
- Hematology
- Urinalysis
- Serum chemistry
- Blood draw for storage
- ASD assessments will be performed, including: ABC, SRS, RBS-R, CGI-S SAS, VAB II, and CGI-I
- Record all adverse events
- Physical exam with vital signs
    - Question caregiver or patient about the patient's week, including questions regarding any changes in home life activities, events at school, sleep, or other matters germane to an understanding of the patient's autistic
    - Record concomitant medications

5.9.3 PATIENTS IN THE ASSIGNED DOSAGE GROUPS

5.9.3.1 Pharmacokinetic Assessments and Sample Handling

In addition to all of the measures listed above, patients in the Assigned Dosage Groups will provide blood at baseline and at each weekly visit to assess the levels of L1-79 for the purpose of understanding the pharmacodynamic profile of t.i.d. L1-79 administration at the specified doses. Similarly, a 24 urine sample will be collected at every visit at which blood samples are collected for PK analysis, treatment visits Weeks 1 through 4.

Blood samples will be drawn, spun down and frozen for shipment to CMIC for assay. 10 a 10 ml aliquots of blood and urine will for pharmacokinetic assay.

Sample collection methods are presented in Appendix D.

5.9.3.2 Electrocardiograms

Patients in the assigned group will receive EKG as specified in section 5.5.2. In the event any EKG abnormalities are noted, additional EKG may be required as described in section 5.5.2.

5.9.3.3 1-week Follow-up visit

- At the request of the FDA, patients in the assigned dosage groups will be followed for at one week while continuing to receive their assigned dose of L1-79 t.i.d. in order to assess the safety parameters described herein before submitting a report describing the results of the safety testing, PK/PD results, and EKG to the FDA for their assessment. For the 100 mg t.i.d. group a favorable review of this report is required to enroll the 200 mg t.i.d. dosage group.

5.9.4 PROVIDING L1-79 SUBSEQUENT TO THIS STUDY

If, in the opinion of the sponsor and the Investigator that L1-79 therapy is well tolerated and provides a beneficial therapeutic effect, an amendment to this study will be considered to provide L1-79 in an open label manner for subjects in this study who have either received placebo or who would likely benefit by receiving additional treatment at the end of the study.

Depending upon the results obtained during this investigation, if warranted, the sponsor may extend this study if the FDA permits. In the event that L1-79 therapy is found appropriate, the sponsor may adjust the dosing consistent with the findings of this trial and continue treating subjects beyond the specified treatment duration herein in a manner compliant with the FDA guidelines.

5.10 Discontinuation of Study Subjects

A patient may be discontinued for the following reasons:

- Non-compliance with treatment regimen or follow up requirements
- Lost to follow-up
- Patient and/or care giver requests voluntary withdrawal
- Adverse event sufficient in the opinion of the Investigator to warrant cessation of treatment
- Adverse event requiring unblinding of the patient's assigned treatment
- Investigator decision

Discontinuation for any reason will be documented in the eCRF and supporting documentation will be added to the patient file. Appropriate treatment will be provided for any disease or syndrome.

All subjects who receive a single dose, irrespective of discontinuation, will be followed for a period of 4 weeks subsequent to the first dose in order to determine whether the treatment was safe.

5.11 Recording of Adverse Events

Each patient will be observed and queried in a nonspecific fashion by the Investigator or designee at each visit during the study for any new or continuing AE that occurs since the previous visit. Any AE reported by the patient or noted by the Investigator or designee will be recorded in the Adverse Event section of the database. The following information will be recorded for each reported AE: description of the event, time of onset, time of resolution, severity, relationship to the study drug determined (as opposed to NSAID or antibiotic related toxicity), outcome, management of the AE, and outcome. Each AE will be classified as serious or not. Serious AE will be handled according to section 5.11.6.

Adverse events will be treated as deemed appropriate by the Investigator and the results will be recorded in the case report form, including any therapeutic regimens prescribed, hospitalization, surgery, discontinuation from the study or any other action related to the adverse event.

The Investigator should use the following definitions to classify the relationship of each adverse experience to the test treatment.

5.11.1 Not Related

This category applies to those adverse experiences that, after careful consideration, the Investigators determines are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

5.11.2 Unlikely: (Must have at least two out of four criteria)

In general, this category can be considered applicable to those adverse experiences that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug. An adverse experience may be considered unlikely to be related if or when:

- The adverse experience does not follow a reasonable temporal sequence* from administration of L1-79 or placebo.
- The adverse experience could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- The adverse experience does not follow a known response pattern to the suspected drug.
- The adverse experience does not reappear or worsen when the drug is re-administered.

*Temporal sequence is defined as an association between the suspect drug and the observed reaction or event in which the suspect drug was present prior to the reaction or event as defined by history or drug blood level.

5.11.3 POSSIBLE: (MUST HAVE AT LEAST TWO OUT OF THREE CRITERIA)

This category applies to those adverse experiences for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration appears unlikely but cannot be ruled out with certainty. An adverse experience may be considered possibly related if or when:

- The adverse experience follows a reasonable temporal sequence from the time of immunization.
- The adverse experience follows a known response pattern to the study drug.
- The adverse experience could have been produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered to the patient.

5.11.4 PROBABLE: (MUST HAVE THREE OUT OF FOUR CRITERIA)

This category applies to those adverse experiences which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study drug. An adverse experience may be considered likely related if or when:

- The adverse experience follows a reasonable temporal sequence from the time of drug administration.
- The adverse experience follows a known response pattern to the study drug.
- The adverse experience cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered to the patient.
- The adverse experience is confirmed by improvement of the symptoms on de-challenge (e.g., the removal withdrawal, or discontinuation of the suspected drug from the patient's therapeutic regimen).

5.11.5 DEFINITE: (MUST HAVE ALL FOUR CRITERIA)

This category applies to those adverse experiences that the Investigator feels are incontrovertibly related to the study drug. An adverse experience may be assigned an attribution of definitely related if or when:

- The adverse experience follows a reasonable temporal sequence from the time of drug administration.
- The adverse experience cannot be reasonably explained by the known characteristics of the patient's state, environmental or toxic factors, or other modes of therapy administered to the patient.
- The adverse experience occurs immediately following study drug administration, or improves on stopping the drug (de-challenge), or reappears on repeat exposure (re-challenge) (Note: this is not to be construed as requiring re-exposure of the patient, however, a category of definitely related can only be used when recurrence is observed).
- The adverse experience follows a known response pattern to the study drug.

5.11.6 ASSESSMENT OF THE SEVERITY OF ADVERSE EVENTS

Severity of an adverse experience is defined as a qualitative assessment of the degree of intensity of an adverse experience as determined by the Investigator or reported to him/her by the patient. The assessment of severity is made irrespective of drug relationship or seriousness of the event using MEDRA criteria.

All serious and life threatening adverse experiences must be reported by entering them into the database and no later than 24 hours after the Investigator has become aware of them. This will generate automatic emails to the study Sponsor and the study monitors. The patient must be monitored carefully until the condition disappears and/or the etiology is defined.

All serious and life threatening adverse experiences must be reported by the Investigator to the appropriate IRB/EC in writing, as well as the study sponsor.

5.12 Recording of Concomitant Therapy

All prescription and nonprescription medication (including vitamins and herbal supplements) taken by the patient from screening to the end of the study will be recorded in the patient's medical record and the eCRF. Any additions, deletions or changes in the dose of these medications should be entered on this form. Generic names should be used to eliminate confusion that may result from trade names. The list of all concomitant medications will be reviewed at each visit, and adjusted as appropriate.

5.13 Study Discontinuation Criteria

The occurrence of a grade 3 or 4 AE in any patient will result in the immediate discontinuation from this study. In the event of a grade 2 AE, the Investigator, at their discretion, may withhold treatment until the event resolves to grade 1 or less.

The Sponsor may at its discretion terminate the study as a whole if conditions warrant this action. The study site Investigator bears responsibility for orderly discontinuation of the study subjects enrolled at his/her study site.

5.14 Dose Adjustment and Stopping Rules

As this is a double-blind trial and the doses administered to a given patient are not known to the Investigator or the sponsor. In the event a grade 1 or 2 adverse event occurs, the regimen will be paused until a resolution of the event occurs and the Investigator feels it is safe to continue. Should the Investigator feel it is not safe to continue, or should the event reoccur that patient will be terminated from this trial and appropriate therapeutic measures taken. Any dosing hiatus or discontinuation will be noted in the case report form.

In the event a patient experiences a grade 3 (Severe) or 4 (Life Threatening) adverse event medication will be discontinued immediately and will not resume until the Investigator and the DMC have agreed that it is safe to do so.

In the event of two grade 3 (Severe) or 4 (Life Threatening) adverse events as found in the schedule of adverse events presented in Appendix A, the study at any site will be stopped until such time as the Principal Investigator, Co-Investigator at that site and the Sponsor have determined appropriate measures to assure the safety of future subjects.

6.0 STATISTICAL PROCEDURES

6.1 Statistical Analysis Plan

Given the size of this initial IND study and the lack of statistical power, descriptive statistic will be used to report the results. A formal statistical plan for the study analyses will be prepared before the treatment portion of the study is completed.

6.1.1 STUDY POPULATIONS

The intent-to-treat (ITT) population will include all randomized subjects. All efficacy analyses will be based on this population.
The safety population will include all subjects who have been received at least one dose of L1-79 or placebo. If all subjects are treated, this population will be identical to the ITT population.

6.1.2 CHARACTERIZATION OF THE STUDY POPULATION

Distributions of the following data will be described by treatment group.

Baseline data:

- Demographics
- Medical history
- Psychometric test scores
- Physical examination parameters
- Vital signs
- ECGs
- Safety labs including hematology and serum chemistry

6.1.3 STUDY CONDUCT

Disposition of all subjects in the study will be summarized including the number of subjects who completed the study as well as the reason for discontinuation for non-completers. The number of subjects in each of the analysis populations, the duration of time on study, and the number of injections will also be displayed. The number and type of protocol violations will be summarized

6.1.4 SAFETY

Adverse events will be coded using MedDRA and will be presented by body system and preferred term. Concomitant medications will be coded using [concomitant medication coding dictionary] and summarized by drug class and generic name.

Tables and graphs will show changes from baseline through 8 weeks of treatment and 26 weeks of follow-up in:

- Physical examination

- Vital signs
- Safety labs, including hematology and serum chemistry
- Cardiovascular changes, including orthostatic blood pressure.
- EKG changes from in the Assigned Dosage Group patients

Other safety data that will be presented include:

- Dose limiting toxicity
- Adverse events along with their severity and potential relationship to study treatment.
- Concomitant medications

6.1.5 EFFICACY ENDPOINTS

6.1.5.1 Main Efficacy Endpoint

The main endpoint will be based upon changes in the CGI, which shall be based on the aggregate of all testing as reviewed and interpreted by the Investigator. Comparisons between the different active treatment arms will be made, as will comparisons between the active treatment arms and the placebo arm.

6.1.5.2 Secondary Efficacy Endpoints

- Analysis of individual psychometric test scores over time
- Multivariate analysis of psychometric test panel over time
- Physicians grading of improvement over time
- Correlations of test scores with each other and with Investigator assessment

6.1.5 OTHER ENDPOINTS

Pharmacokinetic and pharmacodynamic data will be presented for the Assigned Dosage Group patients

7.0 CLINICAL TRIAL SUPPLIES

7.1 Test and Non-Test Articles

The active test article, L1-79 and matching placebo will be supplied to the Investigator as capsules in sealed bottles of 100 capsules of L1-79 or matching placebo. The study pharmacist will allocate the appropriate number of active or placebo into secondary packaging for distribution to subjects.

Each dose will consist of 2 capsules. Doses for subjects in the 100 mg group will be comprised of one 100 mg capsule and 1 placebo capsules while those in the 200 mg group will consist of two 100 mg capsules for each dose.

A drug log will be maintained by the Investigator and all dispensed medications as well as unused medications and those returned by subjects or their caregivers will be logged out and logged in. Empty drug containers will not be returned, but those containing medication will be returned at visits for study weeks 2 and 4 and will be counted, logged in, and stored by the Investigator until the end of the study.

7.2 Preparation of the Study Drugs

The study pharmacist will prepare drugs for dispensing to the subjects to take home. Bottles of 100 capsules will be provided for placebo and 100 mg of L1-79. The pharmacist will package the study medications as individual doses at the study site in the following manner:

7.2.1 ASSIGNED DOSAGE PATIENTS

- At each site, the pharmacist will prepare 44 individual doses (3 doses/d x 14 days + 2 extra doses) with each dose in an individually labeled envelope for six patients (to allow for 1 drop out) in each dosage group. Although not all 5Assigned Dosage Patients in a dosage group will be treated at each site there will be sufficient drug to accommodate all of these patients if one site can enroll faster than another.
- For 2 weeks of daily dosing, each patient would receive 3 x 14 = 42 + 2 extra doses for a total of 44 doses, each dose will be individually packaged in envelopes. The envelopes will be placed in a cardboard box
- Since 2 weeks is the limit for how much drug the FDA guidelines will allow study materials to be packaged in this manner, this process would have to be repeated twice at each study site

7.2.2 RANDOMIZED PATIENTS

- The pharmacist will place individual doses comprised of 2 capsules each in individual envelopes for 12 subjects (to allow for 2 dropouts) in 3 different treatment groups in the following manner:

    - Each dose is comprised of 2 capsules to maintain a double-blind. They are distributed as:
        - Placebo group: 2 placebo capsules
        - 100 mg group: 1 x 100 mg capsule and 1 x placebo
        - 200 mg group: 2 x 100 mg capsule
- For 2 weeks of daily dosing, each patient would receive 3 x 14 = 42 + 2 extra doses for a total of 44 doses, each dose will be individually packaged in envelopes. The envelopes will be placed in a cardboard box
- Since 2 weeks is the limit for how much drug the FDA guidelines will allow study materials to be packaged in this manner, this process would have to be repeated twice at each study site.
- Because of the double-blind nature of the trial, each box is labeled with a sticker that has the study number and patient study number which derives from a random code that links study numbers with dosage groups.

7.3 Dispensing the Study Drug

Study drug will be dispensed as a two week supply during study weeks 0 and 2 visits.. Drugs will be allocated to subjects on a randomized and double-blinded basis. Two containers of 42 doses will consist of the study drug for each patient. Each container will be labeled with the patient's study number.

At the accession visit prior to week 1 and at the post week 2 visit each patient will receive a container of drug corresponding to their study number. Neither the Investigator or the sponsor will know to which dosage group any patient is assigned.

7.4 Labeling of Test Articles

Each drug container will contain 2 weeks of study drug and two extra doses to be used in the event a dose or two is lost, and will be labeled as follows,

- Protocol number
- Storage requirements
- Investigational use statement "Experimental Clinical Use Only"

Each dose consisting of 2 capsules will be individually wrapped and provided within the larger container will be labeled as follows:

Envelope Labels

Protocol HT 02-121
Investigational Drug--Limited by Federal Law to investigational Use

Patient No. XX-YYY

Store at room temperature

Contents:
1 individual dose comprised of 2 capsules each

Take 1 dose of 2 capsules by mouth at upon arising, at 4:00 PM and at bed time. Take with 8 oz. of water.

Batch #: XXXX

Keep out of Reach of Children

Each individual dose will be labeled as follows:

Side of Box

Protocol HT 02-121
Investigational Drug--Limited by Federal Law to investigational Use

Store at room temperature

Take 1 package of 2 capsules by mouth at upon arising, 1 capsule at 4:00 PM and one capsule at bed time. Take with 8 oz. of water.

Keep out of Reach of Children

Top of Box

Patient No: XX-YYY

Study HT 02-121

Box 1 [or 2]
Keep out of Reach of Children

7.5 Storage of Test Article

L1-79 will be stored in a locked and secure cabinet at room temperature. Study drug will be logged out upon dispensing and unused study drug will be returned to the study site and logged in.

7.6 Accountability of Test Article

A dispensing record of test preparations must be maintained by the study site to assure accountability of all medications supplied and administered. The dispensing log must include:

- Amount of study drug dispensed
- Date drug received
- Investigator's signature
- Physical inventory prior to dispensing
- Physical inventory after dispensing

The dispensing record with drug inventory will be reviewed at each monitoring visit.

The L1-79 and placebo supplied for this study is only for use in subjects properly consented and enrolled under this protocol. These drugs must be kept physically separate from standard clinic or office drug supplies.

Unused investigational material will be accounted in the drug log disposed appropriately by the Investigator.

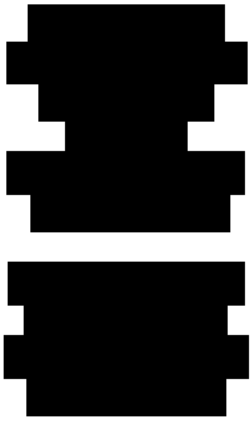
8.0 ADMINISTRATIVE

8.1 Serious Adverse Experience Reporting

A serious adverse experience is defined as any event that results in one of the following outcomes:

- death;
- any life-threatening condition;
- persistent or significant disability/incapacity;
- requires or prolongs inpatient hospitalization;
- a congenital anomaly or birth defect in an offspring of a patient exposed to L1-79 or
- On the basis of appropriate medical judgment, the experience may jeopardize the patient and may require medical or surgical intervention to prevent one of the aforementioned outcomes.

Any serious adverse experience must be reported within 24 hours by entering the information into the appropriate screen in the online data reporting system. This will generate automatic emails to alert the Sponsor and the study monitor contact listed below



After the initial reporting of the experience the following documentation must be entered into the electronic data collection system in the appropriate screen within 5 working days.

- The serious adverse experience form; and
- Any additional documentation (e.g., autopsy report, hospital records, and/or laboratory tests) required to support or add information to the serious adverse experience form. Any such information will be scanned and entered in to the eCRF system to be kept with the patient's records.

All serious adverse experiences must be reported by the Investigator to their IRB in writing, as well as the study sponsor.

8.1.1 NON-SERIOUS ADVERSE EXPERIENCE REPORTING

Non-serious adverse experiences will be reported on the appropriate electronic case report form (eCRF) as described in Section 5.11. The Sponsor is responsible for the reporting of non-serious adverse experiences to the FDA in the IND annual report.

8.2 Electronic Data Collection

Data will be collected via EDC. All data is to be entered within 3 days after each patient evaluation. Data that requires transcription will be transcribed within 3 days.

All entries into the database must be supported by original source documentation (e.g., laboratory reports) maintained at the investigational site.

Correction(s) of data in the database may only be made in a manner that indicates the error and leaves the previous entry identifiable by entering the correct values next to those marked as incorrect. An audit trail will be generated automatically as the data capture system will note the person making a change, the date of the change, and the original information will be maintained as well as the corrected information.

The Investigator is required to review all entries into the database and electronically sign where indicated to attest to the accuracy of the data recorded on the form.

8.3 Investigator Requirements

8.3.1 PRIOR TO STUDY INITIATION

Prior to study initiation, the Investigator will complete and forward the following essential documentation:

- Any and all forms required by local regulatory authorities plus current curriculum vitae for each individual named on the form and/or any other forms required by local regulatory agencies.
- A signed and dated Investigator Agreement Page (Section 10 of the protocol).
- Identification of the clinical laboratory facilities that will be used including certification or proficiency ratings and normal ranges for the determinations described by the protocol and a copy of the curriculum vitae for the lab director. This information will be forwarded to the Data Management group so that the normals are entered into the data management system, and the laboratory documentation scanned and kept within the site information. Any changes in laboratory normals or certifications will be collected and handled in the same manner.
- A copy of the formal written notification of approval of the protocol and consent form to the Investigator from the IRB, in compliance with FDA regulations (The written notification of "Action" is to be signed by the chairman or any persons authorized in the IRB's SOPs).
- A list of institutional review board members and their respective titles, occupations, and institutional affiliations or provide a general assurances number for the IRB.

- An actual copy of the IRB-approved informed consent form and other adjunctive materials to be used in this study to elicit and record patient consent in compliance with Food and Drug Administration (FDA) regulations.
- Documentation to assure local and state regulations has been met, if applicable.

8.3.2 INFORMED CONSENT

The informed consent should be obtained by means of a standard written statement. It should be written to be easily understood by the patient or legal guardian. All aspects of this study including objectives, methods, schedules and so forth should be explained in easy to understand terms, and questions should be elicited and answered in full in order to enable a truly informed consent. The patient/legal guardian should be given the time to read and understand the statement and be afforded the opportunity to ask questions before signing his/her consent and dating the document. The patient/legal guardian should receive a copy of the written statement once she and the Investigator have signed the informed consent.

The informed consent form must be considered as a part of the protocol. It is to be submitted by the Investigator along with the protocol for approval to the IRB.

No study procedures will be initiated prior to obtaining a valid, signed, informed consent.

The informed consent form is presented in Appendix C.

8.3.3 INSTITUTIONAL REVIEW BOARDS (IRB)

The Investigator assures that the Institutional Review Board (IRB) for the initial and continuing review and approval of this clinical study complies with the requirements set forth in 21 CFR Part 56 and all relevant ICH GCP guidelines.

No one may amend this protocol other than the Sponsor. The Investigator also assures that he/she will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research until the IRB has approved the changes, except where necessary to eliminate immediate hazards to human subjects. Documentation of approval or notification must be forwarded to Hoffman Technologies Inc. for any amendment.

The Investigator must also report to his/her IRB at least yearly on the progress of the investigation and obtain written approval to continue the study beyond the time stated in the original approval. The Investigator must notify the IRB of the conclusion of the study within three months after completion, termination or discontinuation of the study. Documentation of the annual progress report to the IRB, renewal of IRB approval, and notification of study conclusion must be maintained in the study files.

8.3.4 RECORDS RETENTION

The sponsor and US Federal law requires that a copy of all records (e.g., informed consent documents, laboratory data slips, source documents, IND safety reports, test article dispensing records, etc.) that support case report forms of this study be retained in the files of the responsible Investigator for a minimum of two years following notification by the sponsor that:

- all investigations at all sites are completed, terminated, or discontinued; or
- the last marketing application in an ICH region (including US Food and Drug Administration) has been approved; and
- There are no pending or contemplated marketing applications in an ICH region.

Study-related records identifying the subject will be kept confidential and, to the extent permitted by applicable law, will not be made public. In the event the results of this study are published all subjects' identity will remain confidential. However, representatives of the U.S. Food and Drug Administration (FDA) will be allowed to examine all patient records under strict confidentiality measures. In addition, representatives of the Sponsor, such as the study monitor, the IRB and possibly representatives of foreign regulatory authorities (should approval of L1-79 be sought in other countries) may also have access to patient records that have been redacted to omit patient identifiers other than the study number and patient initials.

The sponsor may use data generated by this protocol to support regulatory filings in other countries. In order to be in compliance with foreign regulatory agencies, the Investigator is required to maintain all study records for a period of 10 years following the conclusion of this study.

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Hoffman Technologies must be notified in writing of the name and address of the new custodian.

8.3.5 ACCOUNTABILITY AND STORAGE OF TEST ARTICLES

The Investigator is responsible for maintaining an accurate, up-to-date dispensing log for all study drugs supplied by Hoffman Technologies Inc. that includes all of the information presented in section 7.4. All study medication received and dispensed by the Investigator will be inventoried and accounted for throughout the study. The study medication must be stored in a restricted area with limited access. Contents of the study medications of different identities or concentrations must not be combined.

8.4 On-site Monitoring and Audits

The study will be periodically monitored by a representative of the study Sponsor. It is the responsibility of the Principal Investigator to provide all study records, including case report forms, source documents, etc., for review and inspection by the monitor at their

visit. The IRB may also ask to review certain case report forms. Likewise, representatives of FDA may audit the study records including patient records.

The US Food and Drug Administration, in the person of a scientifically trained and properly authorized employee of the agency, may request access to all study records, including source documents, for inspection and copying.

8.5 Amendments to the Protocol

The Sponsor reserves sole authority to amend this protocol, and will not amend or modify the protocol without notifying the Investigator. All amendments must be approved by the study sponsor prior to implementation. The Investigator must attempt to notify the sponsor before submitting all amendments to the IRB for notification and approval. Deviations from the protocol that are required to address immediate patient safety concerns are permitted providing sponsor is notified of such changes prior to their execution.

8.6 Departure from Protocol

Departure from study protocol is not permitted. Should an occasion occur in which the protocol has not been followed, the Investigator is required to provide a written description of the reason(s) that the protocol was not followed and what remedial action will be taken to prevent future occurrences. A note to file should be included in the subject record to provide information about what exactly happened and whether this deviation affected the safety of the patient. In the event an Investigator feels an exemption from this protocol is appropriate the Investigator should discuss a possible waiver with the sponsor.

Repeated departures from the protocol will result in the immediate removal of the Investigator and/or termination of the investigational site. All data collected from such a site will be used to the extent possible, and subjects will be followed for safety as described within this protocol.

8.7 Duration of Trial and Circumstances for Termination

The Investigator agrees to complete their portion of the data entry for this study within 14 days following the final patient's study completion visit.

Extension beyond this timeframe is at the discretion of the study sponsor with consent and approval of FDA and the governing IRB. It is agreed that, for reasonable cause, the Investigator or the sponsor may terminate this study, provided written notice is submitted at a reasonable time in advance of intended termination. The Sponsor reserves the right to terminate the study without advance notice under the following circumstances:

- noncompliance with the protocol;
- slow enrollment (i.e., insufficient to reasonably complete the study within the prescribed timeframe);
- safety concerns,
- manufacturing issues,
- discontinuation of the study protocol,

- discontinuation of all studies of the test drug

In the event of site termination, data collection and entry for treated subjects will continue as described within this protocol.

8.8 Financial Disclosure

As part of the study documentation, the clinical Investigator(s) participating in this study are required to provide sufficient and accurate financial information for the clinical Investigator, their spouse and dependent children to the Sponsor pertaining to:

- Any arrangement between the Sponsor and clinical Investigator whereby the value of the compensation to the clinical Investigator for conducting the study could be influenced by the outcome of the study;
- Any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria
- Any proprietary interest in the tested product held by the Investigator involved in any study
- Any significant equity interest in the Sponsor held by any clinical Investigator involved in the study.

The Investigator will provide this information to the Sponsor at the beginning of the Investigators participation in the study and agree to provide the Sponsor with prompt updates of any relevant changes in financial information for the course of the study and for one year following completion of the study.

INVESTIGATOR AGREEMENT PAGE

I have read the protocol entitled "A Phase 2 Safety Study of L1-79 in the Treatment of Autism" HT 02-121 and agree that it contains all necessary details for performing this study. I will conduct this in compliance with the study protocol, Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines, and all applicable regulatory requirements, and will complete the study within the time designated.

I will provide copies of the protocol and all information on the study drug relating to pre-clinical and prior clinical experience that are furnished to me by the Sponsor to all physicians, nurses and other personnel responsible to me who participate in this study and will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I agree that the conduct and results of this study will be kept confidential. I agree that the case report forms and other data pertinent to this study are property of the study sponsor who may utilize the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of multi-center study, if applicable. I further agree that Hoffman Technologies shall have access to any source documents from which case report form information may have been generated.

I will submit this protocol to my IRB for approval.

_____

Signature

_____	_____	_____
Name	Date	Title

APPENDIX A: STUDY PLAN ACTIVE TREATMENT PHASE

		Visit							
Form #	Form Name	Screening	wk 0 Baseline	Wk 1	Wk 2	Wk 3	Wk 4	1 wk post dosing	4 wk FUP
	Study Day		0 ± 2	7 ± 2	14 ± 2	21 ± 2	28 ± 2	35±2	56 ± 2
1	Date of Visit	x	x	x	x	x	x	x	x
2	Informed Consent & Study Complaince agre	x							
3	Demography	x							
4	Additional Patient Information	x							
5	Inclusion Criteria	x							
6	Exclusion Criteria	x							
7	Eligibility Criteria	x							
8	Medical history	x							
9	Family History	x							
10	Lab - Hematology (all patients)	x					x		x
11	Lab- Serum Chemistry (all patients)	x					x		x
12	Urine Analysis (all patients)	x					x		x
13	Lab - Hematology (Assigned patients only)		x *	x	x	x	x	x**	x
14	Lab- Serum Chemistry (Assigned patients only)		x *	x	x	x	x	x**	x
15	Urine Analysis (Assigned patients only)		x *	x	x	x	x	x**	x
16	PK/PD		x *	x	x	x	x		
17	Blood Draw	x					x	x**	x
18	Vital Signs - screening	x							
19	Vital Signs		x	x	x	x	x	x**	x
20	Physical Examination	x						x**	x
21	Randomization		x						
22	ADOS	x					x		
23	EKG (Assigned patients only)		x	x	x	x	x	x**	x
24	ADI-R (Telephonic)	x							
25	SAS		x					x**	x
26	VABS II		x				x	x**	x
27	ABC-C (all scales)		x	x	x	x	x	x**	x
28	SRS		x	x	x	x	x	x**	x
29	RBS-R		x	x	x	x	x	x**	x
30	CGI-S		x	x	x	x	x	x**	x
31	CGI-I			x	x	x	x	x**	x
32	CGI-Overall score		x	x	x	x	x	x**	x
33	Study Drug dispensing		x		x				
34	Study Drug Administration			x	x	x	x		
35	Drug Accountability				x		x		
36	Adverse Event		x	x	x	x	x	x**	x
37	Prior and Concomitant Medication	x	x	x	x	x	x	x**	x

*At baseline visit for Assigned Group Patients PK samples are to be taken before, and 1 hour after, the 1st dose. ** Assigned Group Patients Only

This schedule describes the study events for each patient on each study day where action is required.

APPENDIX B: STUDY PLAN ACTIVE PLACEBO ROLLOVER PHASE

	Visit			
Form Name	wk 0 Baseline	Wk 2	Wk 4	4 wk FUP
Study Day	0 ± 2	14 ± 2	28 ± 2	56 ± 2
Date	x	x	x	x
Lab - Hematology	x		x	x
Lab- Serum Chemistry	x		x	x
Urine Analysis	x		x	x
Vital Signs	x	x	x	x
Physical Examination	x	x	x	x
ADOS			x	
SAS	x			x
VABS II	x		x	x
ABC-C (all scales)	x		x	x
SRS	x		x	x
RBS-R	x		x	x
CGI-S	x		x	x
CGI-I			x	x
CGI-Overall score	x		x	x
Study Drug dispensing	x	x		
Study Drug Administration	x	x	x	
Drug Accountability		x	x	
Adverse Event	x	x	x	x
Prior and Concomitant Medication	x	x	x	x

APPENDIX C: SUBJECT CONSENT FORM

A Phase 2 Safety Study of L1-79 in the Treatment of Autism

Protocol Version: 48 **Protocol HT 02-121**

Sponsor- Dr. Peter Halas.

«PI_FIRST_NAME» «PI_LAST_NAME»
«PHONE_NUMBER»

Invitation to Participate
Your child is being asked to take part in a research study. Before you decide whether or not your child may take part, it is important for you to understand why the research study is being done and to understand its possible risks and benefits in order to make an informed decision. This process is known as informed consent.

As the parent or legal guardian of a study participant that is not legally permitted to consent to be in a research study on his/her own behalf, it is necessary that you sign this Informed Consent Form.. If there will be a caregiver assisting the child, then the caregiver must sign the Study Compliance Agreement provided separately.

This form gives detailed information about the research study that your study doctor will discuss with you. Once you understand this study, you will be asked to sign this form if you wish your child to participate.

There will be no costs to you for your child's participation in the research study. The Sponsor will cover the costs of the study medication and all study related procedures. If your child's caused injury that is confirmed to be due to his/her participation in the study, the Sponsor will cover all the procedures and/or medications in accordance with the Law.

This study is conducted under an approved FDA Investigation New Drug application. Please read the following information carefully and ask the study doctor listed above for more information if anything is not clear.

<u>Introduction</u>

Dr. Peter Halas is studying a possible treatment for autism. It is an investigational drug named L1-79. An investigational drug is one that is not currently approved by the United States Food and Drug Administration (FDA). L1-79 is very similar to a marketed drug called Demser that was approved by the FDA in 1979. L1-79 has been tested in animals and found to be safe at doses higher than those used in this trial. It has been used experimentally to treat cancer

subjects in combination with other agents and has been well tolerated. L1-79 has also been given to a small number of subjects with autism and has also been safe and well-tolerated in these subjects.

Historically Demser has been shown to be safe in higher amounts when taken for the duration of time you will be taking L1-79. Although the L1-79 has been used in people before on a very limited basis, it has been tested in a number of animal species, including dogs, and shown to be safe at doses much higher than those your child will be exposed to.

L1-79 has already been given to a small number of children with autism and without adverse events. It is not known if this treatment will benefit everyone, which is why we are testing it with your child. Your child's doctor believes that this medication may help your child, and that is why he/she has been selected to participate in this study if you agree to your child's participation.

The study you are considering for your child is the first time L1-79 has been administered to people with autism under strict clinical trial guidelines. A total of 40 people with autism will participate in this study. Participants will receive either 200 or 100 mg of L1-79 three times a day or a sugar pill three times daily for 28 days (4 weeks). Your child will be randomly assigned by chance (like the flip of a coin) to receive either the study medication or sugar pill. For each patient randomly assigned to receive placebo, 2 patients will be randomly assigned to receive L1-79. Neither you or your child, nor the study doctor will know which of these treatments your child receives. In case of an emergency, however, the study doctor can get this information. During the study your child will receive one of the two amounts of L1-79 or sugar pill for 4 weeks during which your child will return to the clinic 4 times followed by 4 more weeks of observation without L1-79 during which your child will return twice to the doctor. Some patients may also have an additional visit to be evaluated at 1 week after dosing.

The risks and benefits of this study are explained below.

Purpose

The purpose of this study is to determine if the drug called L1-79 is safe in the manner that it is given in this study, and to see if it has a beneficial effect on the symptoms of autism.

Procedures

Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. Over the course of the study staff will measure and record blood pressure, heart rate, breathing rate, body temperature, height and weight, and blood and urine samples will be taken. Blood samples for determining drug levels in the blood will be taken at each study visit for some patients depending on their group assignment. You will be informed if your child is one of those patients. Electrocardiograms will be taken weekly for some patients. You will be informed if your child will be one of those patients. The doctor will ask you questions about your child's medical history and any medications that your child is

currently taking to make sure that he/she meets the requirements of this research study. In addition, different question and answer tests will be taken during this study.

You will be given capsules of L1-79 to take home. The study doctor or the doctor's staff will follow your child for any adverse effects that he/she may experience after he/she receives the study medication. You agree that your child will take the study medication as directed, 3 times per day for 28 days. One dose will be taken upon arising, one at approximately 4 pm, and one dose will be taken at bedtime.

It is important that you keep unused study medication out of the reach of children and those of limited ability to understand and that the study medication is only taken by the research participant.

If your child takes part in this research study they will have the following tests and procedures:

- Blood tests to follow blood counts (red cells, white cells and platelets) and to monitor his/her body function such as liver function and kidney function. Approximately three (3) tablespoons of blood will be drawn at the beginning to see if your child qualifies for the study and at week 4 after starting the study so that the doctor can perform laboratory studies to check the blood levels of certain chemicals in your child's body.

- Some patients will have blood taken to analyze the amount of the study drug that is in the blood.

- Also, at the same time, another 3 tablespoons of blood will be taken and stored frozen for use in future analysis in order to determine if changes seen in blood chemicals correspond to changes in your child's disease. Samples will be stored frozen labelled with only the protocol and patient numbers, for up to 7 years after which time they will be destroyed. However, once the samples have been analyzed, the data will be stored in a confidential manner and consent may no longer be withdrawn. It is not known when these samples will be used nor what analyses will be performed. However, you may refuse to allow these blood samples to be used in this procedure and your child's blood will not be stored. Furthermore, you may withdraw consent for use of your child's blood samples at any time (even after the blood samples have been stored) by speaking with the study doctor listed on page one of this informed consent or a member of his staff and your child's participation in the study will not be jeopardized in any way. If requested, the samples will be destroyed and any data removed from the database.

- Urine analysis to determine if any abnormalities occur in the urine

- Physical examinations

- Standard tests used to measure the symptoms of autism will be completed that assess the state of your child's disease in order that changes in his/her performance can be determined.

Your will be required to provide your child's current address and telephone number to the study doctor and to update this information throughout the research study so that the doctor or the doctor's staff will be able to contact you with any new information. It will be very important that you keep all follow up visits to the study doctor.

Risks

L1-79 has not yet been approved for human use, although it has been tested in various animals including dogs and found to be safe at doses considerably higher than those used in this study.

L1-79 has the same chemical structure as Demser, which has been on the market and shown to be well tolerated at doses that correspond to the dose your child will receive. Demser® is used in the treatment of patients with a cancer called pheochromocytoma (a tumor or tumors found in the adrenal glands which sit atop the kidneys). Demser uses a formulation of this chemical that has greater biological activity and a shorter time in the body than L1-79, and has not been found to be effective in treating autism.

The doses of Demser used to treat cancer are higher than those used in this study. Historically, some persons with pheochromocytoma who have taken Demser have reported various side effects. The doses administered to these patients however is greater than the dose administered in this study and Demser has a greater biologic effect than L1-79. The toxicity reported for Demser includes:

Possible

- Moderate and severe sedation is reported most commonly but seems to wear off after a few days
- Kidney stones been found in dogs treated with Demser at doses similar to those used in humans, and have also been observed in a few patients at the higher doses of Demser**.**
- Drooling, speech difficulty, and tremor have been reported in approximately 10 percent of patients at the higher dosages.
- Anxiety and psychic disturbances such as depression, hallucinations, disorientation, and confusion may occur which increases with the dose given.
- Dose related diarrhea occurs in about 10 percent of patients and may be severe.
- Other dose related adverse events include:
    - Fatigue
    - Increase energy
    - Back pain
    - Breast pain
    - Itching
    - Excessive sweating
    - Tremor
    - Anxiety

- Crystalluria (tiny crystals in urine)

Rare

- Slight swelling of the breast, nasal stuffiness, decreased salivation, dry mouth, headache, nausea, vomiting, abdominal pain, and impotence or failure of ejaculation may occur. Transient episodes of inability to urinate or blood in the urine have been observed in a few patients.
- Hematologic disorders (including changes in blood counts, changes in liver enzymes and swelling and redness in the throat have been reported rarely.

It should be noted that none of these events have been seen in any of the patients treated with L1-79 at the doses used in this study. L1-79 has been tested in a small number of subjects with cancer and it was well tolerated.

Two of the subjects went to bed early on the 1st day of treatment, which is considered to be mild sedation which may have been caused by L1-79, but this only occurred on day 1 of treatment. If your child experiences any pain, discomfort, or unusual health related condition you should discuss these with the study doctor or your child's primary doctor. It will be important to maintain hydration of the patient during the treatment period. There may also be other side effects that we cannot predict. Many side effects are short lived and go away within hours. This is a new drug and not many people have received L1-79 and not all possible side effects may be known at this time.

Your child should exercise special caution when driving, riding a bike or using machinery since the study drug may cause drowsiness, lack of coordination or slowed reaction time.

Rarely, allergic reactions can be life threatening but treatment for this will be available. If any side effects appear in other subjects in this study you will be informed of these as they occur. If information becomes available that may affect your willingness to allow your child to participate in or continue your child's participation in this study, you will be informed immediately.

If your child receives placebo, your child's condition will not be treated with active medication and may become worse, stay the same or improve.

Risks of Study Procedures

•Blood samples: possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.

•ECG: Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.

Unforeseen Risks
Since the study drug is investigational when taken alone or in combination with other medications, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening.

Other treatment
Your child does not have to be in this study to receive treatment for his/her autism**.** You may continue to see the study doctor and have your child receive treatment and continued evaluation without agreeing to participate in this study. The study doctor will discuss with you the risks and benefits of the alternative treatments.

New Findings
Any new important information that is discovered during the study and which may influence your willingness to continue your child's participation in the study will be made available to you.

Costs and financial risks
There will be no costs to you or your child for participating in this study. The study medication L1-79 and all of the care your child receives during this study will be provided free of charge.

Compensation
You will not be paid or compensated for expenses associated with your child's participation in this study, nor will you be reimbursed for any travel costs associated with attending the clinic.

Benefits
If you agree that your child takes part in this study, there may or may not be direct medical benefit to your child during the time he/she is receiving treatment. It is unknown if any benefit will last after the four weeks of treatment. Benefits might include increased ease in social situations, reduced irritability and anxiety, better ability to converse, and possibly other benefits. The information learned from this study may benefit other subjects with autism in the future.

Confidentiality

Every attempt will be made by the Investigators to maintain all information collected in this study strictly confidential, except as may be required by court order or by law. The study doctor, authorized representatives of the Sponsor, Dr. Peter Halas as well as the Food and Drug Administration (FDA) and the Institutional Review Board (IRB), will be able to have access to, and may copy, confidential study-related records from your child's participation in the study. This means that absolute confidentiality cannot be guaranteed. Only your child's initials and a unique study specific identification number will link your child to the information collected. Any additional information collected will not be used for any purpose except reporting to the regulatory agency.

This access is necessary to insure the accuracy of the findings and your child's safety and welfare. If any publication or presentations result from this research your child will not be identified by name.

Compensation for Injury

If your child is injured as a result of taking the study drug(s) or from procedures done for the purpose of this study, the sponsor will pay for those medical expenses necessary to treat your child's injury that are not covered by your medical insurance or any other third party coverage. There are no plans to provide other compensation beyond that which is listed in this informed consent document. Your child will not lose any of his/her legal rights or release the Sponsor, the study doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent document.

If your child is injured during this study, the study doctor will discuss with you the available medical treatment options.

Emergency Contact/IRB Contact

During the study, if your child experiences any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care for your child, or hospitalization is required, alert the treating physician that he/she is participating in a research study being conducted by the study doctor listed on page one of this document.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your child's rights as a research subject, and/or concerns or complaints regarding this research study, you should write to Schulman IRB, 4445 Lake Forest Drive Suite 300, Cincinnati, Ohio 45242, or call toll-free 1-888-557-2472 during business hours Monday - Friday 8:00 a.m. to 6:00 p.m. EST.

Disclaimer/Withdrawal

Your child's participation in this study is voluntary. You can choose for your child not to take part in the study, or can withdraw your child at any time. Your child will not lose any benefits to which he/she is otherwise entitled. If you withdraw your child from the study your child can continue to receive treatment for his/her condition from their primary physician. Your child will not be prevented from participating in future studies.

Your child may be asked to leave the study by the study doctor or the Sponsor, Dr. Halas, without your consent at any time during the study for any of the following:

- If your child needs other treatment,
- If your child does not follow the study plan,
- If your child has a study related Injury/Complication,

- Because the entire study has been stopped,
- If your child's doctor feels that it is in your child's best interest,
- Or for any other reason relevant in the opinion of your child's doctor or the study Sponsor.

If your child leaves the study, the study doctor may ask to examine your child and to perform some final tests.

PRIMARY CARE PHYSICIAN / SPECIALIST NOTIFICATION OPTION

Please indicate below whether you want us to notify your child's primary care physician or your child's specialist of their participation in this study.

_____ Yes, I want the study doctor to inform my child's primary care physician/specialist of their participation in this study.

_____ No, I do not want the study doctor to inform my child's primary care physician/specialist of my child's participation in this study.

_____ I do not have a primary care physician/specialist for my child.

_____ The study doctor is my child's primary care physician/specialist.

Consent

I have read and understand the consent form. I agree to allow my child to participate in this research study. I voluntarily agree for my child to participate in this study until I decide otherwise. I do not give up any of my child's legal rights by signing this consent document. Upon signing below, I will receive a signed and dated copy of the consent form.

_____

Print Subject's Name (For all subjects between 13 to 21 years of age)

_____

Printed Name of Parent or Legal Guardian*

_____ _____

Signature of Parent or Legal Guardian* Date

***By signing this consent document, I verify that I have the legal authority (legal custody) to give permission for this child to participate in this study.**

To be completed by the Study Site

_____

Name of Person Conducting the Consent Discussion
(Please Print)

_____ _____

Signature of Person Conducting the Consent Discussion Date

_____ _____ _____

Name of Investigator (if different from above) Signature of Investigator (if different from above) Date/Time

CONSENT FOR PARENTS OR LEGAL GUARDIAN WHO CANNOT READ

The parent or legal guardian of the study subject has indicated that he/she is unable to read. The consent document has been read to the parent or legal guardian by a member of the study

staff, discussed with the parent or legally authorized representative by a member of the study staff, and the parent or legal guardian of the subject has been given an opportunity to ask questions of the study staff.

_____
Printed Name of Impartial Witness

_____ _____
Signature of Impartial Witness* Date

*Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the subject. **Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance**

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

During your child's participation in this research study, the study doctor and study staff will collect or create personal health information about your child (for example, medical histories and results of any tests, examinations or procedures your child undergoes while in the study) and record it on study documents. The study doctor will keep this personal health information in your child's study-related records (that we will refer to as "your child's study records"). In addition, the study doctor may obtain, and include in your child's records, information regarding your child's past, present and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your child's medical records from your child's doctor. Your child's study records may include other personal information (such as social security number, medical record numbers, date of birth, etc.), which could be used to identify your child. Health information that could identify your child is called "Protected Health Information" (or "PHI").

Under federal law (the "Privacy Rule"), your child's PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission. This permission is called an "Authorization". Therefore, your child may not participate in this study unless you give your permission to use and disclose their PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor and staff to use your child's PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor to disclose PHI as described below:

- The sponsor of this study and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures and commercial products. The study staff will assign a code number and/or letters to your child's records, which means that your child will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at your child's complete study records that identify your child. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review your child's PHI during these visits to make sure the information is correct.
- The Institutional Review Board ("IRB") may have access to your child's PHI in relation to its responsibilities as an Institutional Review Board.

The study doctor or sponsor may disclose your child's PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

Except for the disclosures described above, your child's PHI will not be shared with others unless required by law. If your child's PHI is given to the parties listed above and/or to others who are not required to comply with the federal law, your child's PHI will no longer be protected by this law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your child's PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your child's PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your child's records.

This Authorization will expire 50 years from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your child's PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need

the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor, stating that you are revoking your Authorization to Use and Disclose Protected Health Information for your child. If you revoke this Authorization, your child will not be allowed to continue to be in this study.

You will receive a copy of this Authorization after you have signed it.

_____
Printed Name of Subject (For all subjects between 13 to 21 years of age)

_____
Printed Name of Parent or Legal Guardian*

_____ _____
Signature of Parent or Legal Guardian* Date

***By signing this consent document, I verify that I have the legal authority (legal custody) to give permission for this child to participate in this study.**

To be completed by the Study Site

_____
Printed Name of the Person Obtaining the Authorization

_____ _____
Signature of the Person Obtaining the Authorization Date

_____ _____ _____
Name of Investigator (if different from above) Signature of Investigator (if different from above) Date/Time

FOR SUBJECTS WHO CANNOT READ

The study subject or legal guardian has indicated that he/she is unable to read. This Authorization document has been read to the subject or legal guardian by a member of the study staff, discussed with the subject or legal guardian by a member of the study staff, and the subject or legal guardian has been given an opportunity to ask questions of the study staff.

_____
Printed Name of Impartial Witness

_____ _____
Signature of Impartial Witness* Date

*Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the subject. **Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance**

APPENDIX D: STUDY COMPLIANCE AGREEMENT

A Phase 2 Safety Study of L1-79 in the Treatment of Autism

Protocol HT 02-121

Sponsor- Dr. Peter Halas

«PI_FIRST_NAME» «PI_LAST_NAME»
«PHONE_NUMBER»

I,_____ am the care giver for _____
and will provide care for this patient over the course of the clinical trial "A Phase 2 Safety Study of L1-79 for the Treatment of Autism". In this capacity I agree to the following as my participation in this study.

- I will assure that the above named patient attends all regularly scheduled study visits in a timely manner,
- I will attend all scheduled clinic visits with the patient, or, if I am not available, I will make sure that a responsible surrogate is present with the patient at each visit.
- I will assure that all unused medication will be returned at the 2 and 4 week visits

Name of Caregiver	Signature of Caregiver	Date/Time
Name of Person Obtaining Agreement	Signature of Person Obtaining Agreement	Date/Time
Name of Investigator (if different from above)	Signature of Investigator (if different from above)	Date/Time

APPENDIX E: SAMPLE COLLECTION METHODS

Blood Collection Methods

1. Collect blood in a red top Vacutainer tube.
2. Invert 8-10 times
3. Allow to clot for 30-45 minutes at room temperature
4. Centrifuge for 1,000 – 2,000 RPM for 10 minutes in a refrigerated centrifuge
5. Pipette supernatant into cryovials in 0.2 ml aliquots,
6. Store immediately at -70^{o}C

Urine Sample Collection

A 24 hour urine specimen is required. This is done by pooling all urine collected in a 24 hour period as described below.

On the day of the collection, discard the first morning urine void, and begin the collection after this void. Collect all urine for the next 24 hours so that the morning urine void on the second day is the final collection. Measure and record this volume on the test request form and on the urine transport vial (see Pediatric Specimen Tubes below). Transfer a 10 ml volume into the labeled urine transport vial.

Do not send the entire urine collection.

APPENDIX F: DSM-5 DIAGNOSTIC CRITERIA FOR AUTISM SPECTRUM DISORDER

http://www.cdc.gov/ncbddd/autism/hcp-dsm.html

Diagnostic Criteria for 299.00 Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text):
    1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
    2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
    3. Deficits in developing, maintaining, and understand relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):
    1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
    2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g. indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

- With or without accompanying intellectual impairment
- With or without accompanying language impairment
- Associated with a known medical or genetic condition or environmental factor
- (Coding note: Use additional code to identify the associated medical or genetic condition.)
- Associated with another neurodevelopmental, mental, or behavioral disorder
- (Coding note: Use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].
- With catatonia (refer to the criteria for catatonia associated with another mental disorder)

- (Coding note: Use additional code 293.89 catatonia associated with autism spectrum disorder to indicate the presence of the comorbid catatonia.)